COMPARISON ON EFFICACY AND SAFETY OF LINAGLIPTIN Vs. SITAGLIPTIN AMONG TYPE 2 DIABETIC PATIENTS

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

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In

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By

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CERTIFICATE

This is to certify that, this thesis work entitled **"COMPARISON ON EFFICACY AND SAFETY OF LINAGLIPTIN Vs. SITAGLIPTIN AMONG TYPE 2 DIABETIC PATIENTS"** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmacy Practice of The Tamil Nadu Dr. M.G.R Medical University, Chennai is a bonafide work carried out by **Reg No.261240251** and was guided and supervised by me during the academic year April 2013- 2014.

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DECLARATION

I hereby declare that this thesis work entitled **"COMPARISON ON EFFICACY AND SAFETY OF LINAGLIPTIN Vs. SITAGLIPTIN AMONG TYPE 2 DIABETIC PATIENTS"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai, was carried out by me in the Department of Pharmacy practice, Ultra College of Pharmacy, Madurai, under the valuable and efficient guidance of **Mr.S.K.Sathish, M.Pharm,** Department of pharmacy practice, Ultra College of Pharmacy, Madurai during the academic year April 2013- 2014. I also declare that the matter embodied in it is a genuine work and the same has not to form the basis for the award of any degree, diploma, associateship, and fellowship of any other university or institution.

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INTRODUCTION

1. DIABETUS MELLITUS

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs.[1]

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment cause death. The long term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.[1]

In the human body a number of systems and pathway's function in synchrony to bring about and maintain a healthy physiological state. At the core of these processes lies the ability of the organism to maintain a constant stable state or homeostasis. An aberration of the homeostasis leads to the development of an injury or a pathological state in various organs.DM reduces the ability of an individual to regulate the level of glucose in the blood stream resulting in a number of major some minor complications.[2]

2. HISTORY

Diabetes mellitus was recognized as early as 1500 B.C.by Egyptian physicians, who described a disease associated with "the passage of much urine. "The term "diabetes"(the Greek word of siphon) was coined by the Greek physician Aretaeus the cappadocian around A.D.2.Aretaeus noticed that patients with diabetes had a disease that caused the siphoning of the structural components of the body into the urine("a melting down of the flesh limbs into the

urine").Although it was known for centuries that the urine of the patients with diabetes was sweet, it was not until 1674 that a physician named willis coined the term "diabetes mellitus"(from the Greek word for honey).[3]

3. EPIDEMIOLOGY AND PREVALENCE OF DIABETES MELLITUS.

Epidemiology provides a scientific basis for clinical and public health practice.Indeed, epidemiology can be used to guide how we define, diagnose, and screen for diabetes, to describe the present and future burden of diabetes, and to highlight opportunities for intervention.[4]

Diabetes mellitus and its complications are now the third leading cause of death in the United States, accounting for 300,000 lives in each year. Patients who are diagnosed with diabetes include 2.8% of the U.S. population but account for 5.8% of total personal health care expenditures in 1992.seven to eight percent of hospital admissions are due to diabetes. A new case of diabetes is diagnosed every 60 seconds, and the chance of developing diabetes doubles with every 20% of excess weight and every decade of life.[3]

Both the incidence and prevalence of diabetes increase dramatically with age. For example, the prevalence of self-reported diagnosed diabetes is 1.7% among persons 20 to 39 years of age and 15.8% among persons over 65 years of age. Onestudy estimates that the prevalence of diabetes in persons over 65 years of age increased 62% from 2003 to 2004.The prevalence of type 2 diabetes also differs among ethnic population.[5]

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the diabetes atlas 2006 published by the international diabetes federation, the number of people with diabetes in india currently around 40.9 million is expected to rise to 69.9million by 2025.[6]

World Health Organization to project the number of persons over the age of 20 with diabetes in the world in the years 1995,2000,and 2025.We projected that the number of adults with dsiabetes would increase by 42% in developed countries,from51 million to 72 million, and 170% in developing countries, from 84 million to 228 million.[4]

4. CLASSIFICATION[1, 7]

Diabetes mellitus classified as

I. Type 1 diabetes mellitus.
- A. Immune mediated.
- B. Idiopathic.

II. Type 2 diabetes mellitus.

III. Other specific types of diabetes.
- A. Genetic defects of β-cell function.
- B. Genetic defects in insulin action.
- C. Disease of the exocrine pancreas.
- D. Endocrinopathies.
- E. Drug or chemical induced.
- F. Infections
- G. Uncommon forms immune-mediated diabetes.
- H. Other genetic syndromes sometimes associated with diabetes.

IV. Gestational diabetes mellitus.

I. TYPE 1(IDDM)[1,7,8]

The β-cell destruction, usually leading to absolute insulin deficiency.

Signs and symptoms

- Polyuria, polydipsia, polyphagia, thirst.
- Weakness or fatigue.
- Weight loss associated with random plasma glucose≥200 mg/dl.
- Ketonemia, ketonuria, or both.
- Islet autoantibodies are frequently present.

Pathophysiology

A. Immune mediated diabetes

This form of diabetes, which accounts for only 5-10% of those with diabetes, previously encompassed by the terms insulin dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated auto immune destruction of the pancreas. Markers of the immune destruction of the cell include islet cell autoantibodies, autoantibodies

to insulin, autoantibodies to glutamic acid decarboxylase (GAD_{65}) and auto anti bodies to the tyrosine phosphatases IA-2 and IA-2β.one and usually more of these autoantibodies are present in 85-90% of individuals when fasting hyperglycemia is initially detected. Also the disease has strong HLA association, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective.

In this form of diabetes, the rate of-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults).some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this later stage of the disease, there is little or no insulin secretion as manifested by low or undetectable levels of plasma C-peptide. Immune mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8^{th} and 9^{th} decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined.

B. Idiopathic diabetes

Some forms of type 1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited lacks immunological evidence for β-cell auto immunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients.

II. TYPE 2(INDDM)

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance.

Signs and symptoms

- Polyuria and thirst.
- Weakness or fatigue.
- Recurrent blurred vision.
- Vulvovaginitis or pruritus.
- Peripheral neuropathy.
- Often asymptomatic.[8]

Pathophysiology

This form of diabetes, which accounts for 90-95% of those with diabetes, previously referred to as non-insulindepedent diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative(rather than absolute)insulin deficiency At least initially, and often throughout their life time, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below.[7]

Most individuals with type 2 diabetes exhibit abdominal obesity which itself causes insulin resistance. In addition, hypertension, dyslipidemia (high triglycerides levels and low HDL-cholesterol levels), and elevated inhibitor plasminogen activator-1(PAI-1) levels are often present in these individuals. This clustering of abnormalities is referred to as the "insulin resistance syndrome" or the metabolic syndrome. "Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing macrovascular complications. Type 2 diabetes has a strong genetic cause of most cases of type 2 diabetes.[9]

III. OTHER SPECIFIC TYPES.[1, 7]

A. **Genetic defects of β-cell function.**
   - Chromosome 12,HNF-1α(MODY3)

- Chromosome 7,glucokinase(MODY2)
- Chromosome 20,HNF-4α(MODY1)
- Chromosome 13,insulin promoter factor-1(IPF-1;MODY4)
- Chromosome 17,HNF-1β(MODY5)
- Chromosome 2,NeuroD1(MODY6)
- Mitochondrial DNA

B. Genetic defects in insulin action.

- Type A insulin resistance.
- Leprechaunism
- Rabson-Mendenhall syndrome
- Lipoatrophic diabetes

C. Diseases of the exocrine pancreas.

- Trauma/pancreatectomy
- Pancreatitis
- Neoplasia
- Cystic fibrosis
- Hemochromatosis
- Fibrocalculouspancreatopathy

D. Endocrinopathies.

- Acromegaly
- Cushing's syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma

E. Drug-or chemical-induced.

- Vacor
- Pentamidine
- Nicotinic acid
- Glucocorticoids
- Thyroid hormones
- Diazoxide
- β-adreneergic agonist
- Thiazides
- α-interferon

F. Infections

- Congenital rubella
- Cytomegalo virus

G. Uncommon forms of immune-mediated diabetes.

- "stiff-man"syndrome
- Anti-insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes.

- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome

- Wolfram's syndrome
- Friedreich's ataxia
- Huntington's chorea
- Laurence-moon-biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome

IV. Gestational diabetes mellitus.

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.

DIAGNOSIS (OR) SCREENING METHOD

The term **diagnosis** refers to confirmation of diabetes in people who have symptoms, or who have had a positive screening test. In diabetes, the screening test may be the diagnostic test.[10]

Diagnosis of diabetes is done by measuring blood/plasma glucose level.[1]

Oral Glucose Tolerance Test (OGTT):

The test should be preceded by an overnight fast of 8-14 hours, a morning fasting blood sugar is drawn and patients ingest a 75g glucose load. Then blood samples are drawn at half an hour intervals for 2 hours and then at 3 hours. In normal subjects, the blood glucose returns to normal in less than 2 hours. The normal and up normal OGTT are[1]

2-Hour post load plasma glucose (oral glucose tolerance test)

Normal	=<140mg/dL (7.8mmol/L)
Impaired glucose tolerance (IGT)	=140-199mg/dL (7.8-11.1 mmol/L)
Diabetes mellitus	=≥200mg/dL(11.1 mmol/L)[9]

Fasting plasma glucose (FPG):

Blood is drawn from the overnight fast. The diagnosis of diabetes mellitus may be confirmed in the patient with two or more fasting plasma glucose levels.[1]

Fasting plasma glucose (FPG)

Normal	=FPG<100 mg/dL (5.6 mmol/L)
Impaired glucose tolerance (IGT)	=100-125 mg/dL (5.6-6.9 mmol/L)
Diabetes mellitus	=FPG ≥126mg/dL(7.0 mmol/L)[9]

Glycosylated hemoglobin (HbA1c)

Glycated hemoglobin (AIC) is a valuable indicator of treatment effectiveness, and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted. HbA1C is a reliable estimate of mean plasma glucose (PG) levels over the previous 3 to 4 months for most individuals.[11]

Since glycation of hemoglobin occurs only as the erythrocyte circulates in serum, hemoglobin in the older erythrocytes is more glycosylated; hemoglobin in the reticulocyte is less. Total HbA1c reflects them is of older and younger erythrocytes. Therefore, if the average life of red cells is abnormally short.[12]Glycemic control is defined as if the measured HbA1c; [13]

Excellent	=<6.5%
Very good	= 6.5 to 7.0%
Good	=7.1 to 7.5 %
Acceptable	=7.6 to 8.0 %
Poor	= > 8.0 %

COMPLICATIONS

Diabetes is associated with an increased risk of developing vascular complications that contribute to morbidity and mortality of patients. Poor glycaemic and blood pressure control lead to vascular complications that affect large (macrovascular), small (microvascular) vessels, or both.[2]

The importance of protecting the body from hyperglycemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both type 1 and type 2 diabetes. Generally, the injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy)[14]

Hyperglycemia is considered a major factor in the development of diabetic complications and the adverse effects are recognizable through multiple pathways. The aldose reductase (polyol) pathway, advanced glycation end-product pathway, hexosamine pathway, and protein kinase C pathway provide evidence that elevated blood glucose promotes cellular dysfunction and damage.[15]

MICROVASCULAR COMPLICATIONS

Microvascular complications involve damage to the small blood vessels and contribute to diabetic neuropathy (nerve damage,), nephropathy (kidney disease) and retinopathy (eye disease).[2]

In fact, macrovascular complications can begin developing at least 7 years before the clinical diagnosis of type 2 diabetes.[15]

Diabetic Retinopathy

Diabetic retinopathy, caused by damage to the retinal vasculature, is a common cause of blindness and visual impairment in the working age population. The occurrence of diabetic retinopathy can be reduced and / or prevented by adequate and timely treatment.[2]

Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K.[14]

Aldose reductase pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism.[14]

Early detection and timely treatment of diabetic retinopathy can prevent loss of vision. Many people are not receiving recommended eye care for diabetic retinopathy. Various public health programs have been developed to overcome barriers to optimal eye care.[16]

Diabetic Neuropathy

Diabetic neuropathy classified as peripheral, proximal, focal and autonomic, is the most common of all the log-term complications of diabetes, with nearly 60% of patients having some form of nerve damage. It is a progressive disease that involves loss of sensation, as well as pain and weakness, and can lead to limb amputations.[2]

Physical examination reveals sensory loss to light touch, vibration, and temperature. Abnormalities in more than one test of peripheral sensation are >87% sensitive in detecting the presence of neuropathy.[14]

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of end – stage renal disease (ESRD) and the most common cause for kidney transplantation in the developed world. The presence and progressive rise of albumin in urine along with elevated glomerular blood pressure are the biomarkers of nephropathy. In the absence of appropriate intervention, the condition persists and leads to the loss of protein in urine and a decline in renal function in the form of lower glomerular filtration rate. This eventually leads in ERSD and complete renal failure. Clinical evidence suggests that approximately 15-20% of patients with T1DM and 30-40% with Type 2 develop ESRD.[2]

Microalbuminuria is defined as albumin excretion of 30-299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy.[14]

MACROVASCULAR COMPLICATIONS

The macrovascular complications, which affect the large vessels of the circulatory system may lead in 2 to 4 times higher incidence of stroke (cerebrovascular), coronary heart disease (CHD) and peripheral vascular disease which can lead to ulceration, gangrene and lower extremity amputations. These macrovascular complications are essentially accelerated forms of atherosclerosis involving the migration of leukocytes to site of arterial injury.[2]

The risk of macrovascular complications is increased by other factors such as arterial hypertension, dyslipoproteinaemia or obesity, which are frequently associated with diabetes.

These 'risk factors' have both genetic and environmental backgrounds, which contribute to accelerated manifestation of cardiovascular disease.[17]

The central pathological mechanism inmacrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system.[14]

Cardiovascular:

People with diabetes are 2 to 4 times more likely to develop cardiovascular disease (CVD) than those without diabetes. However; the risk of coronary artery disease is increased in patients with poor glycemic control. In patients with insulin resistance, the disease tends to accelerate to atherogenesis long before the onset of hyperglycemia. There are several risk factors that may contribute to the development of coronary heart disease (CHD), including lifestyle (e.g., cigarette smoking and diet), hyperglycemia, hypertension, and high cholesterol.[15]

Cerebrovascular:

Cerebrovascular disease is a term encompassing many dis orders that affect the blood vessels of the central nervous system. These disorders result from either inadequate blood flow to the brain (i.e. cerebral ischemia) or from hemorrhages into the parenchyma or subarachnoid space of the central nervous system (CNS). Various terms have been used to describe cerebrovascular events. For example, the term transients ischemic attack (TIA).[15]

Peripheral Arterial Disease (PAD):

Peripheral arterial disease (PAD) is an atherosclerotic occlusive disease. It is the major risk factor for lower extremity amputations. The abnormal metabolic state accompanying diabetes results in changes in the state of arterial structure and function predisposing people.[15]

Elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, apolipoprotein B, lipoprotein (a), and plasma viscosity are potential risk factors for PAD.[15]

The 2 Cardinal symptoms of PAD are intermittent claudication and pain at rest. Intermittent claudication is characterized by pain, ache, a sense of fatigue, or other discomfort that occurs in the affected leg during exercise, particularly walking, and resolves with rest.[15]

MANAGEMENT OF DIABETES

The main aim in the management of diabetes is to maintain blood glucose levels as near to normal as possible, while avoiding hypoglycaemia. In order to achieve this, there are five tools involved in diabetes treatment which are education, exercise / activity, diet, oral medications and or insulin, often used in combination.[2]

The primary goals of DM management are

To reduce the risk for microvascular and macrovascular disease complications.

- To ameliorate symptoms.
- To reduce mortality.
- To improve quality of life.[9]

The goal achieved by non-pharmacological and pharmacologic management.

NON PHARMACOLOGIC THERAPY

Self-management education (SME):

Self-management education (SME) that incorporates knowledge and skills development, as well as cognitive behavioral interventions, should be implemented for all individuals with diabetes. The content of SME programs must be individualized according to the individual's type of diabetes, current state of metabolic stability, treatment recommendations, readiness for change, learning style, ability, resources and motivation.

SME is a fundamental component of diabetes care and is most effective when ongoing diabetes education and comprehensive healthcare occur together.[18]

Make patient-centered, structured self-management education an integral part of the care of all people with type 2 diabetes.[19]

Role of clinicians in promoting self-care is vital and has to be emphasized. Realizing the multifaceted nature of the problem, a systematic, multi-pronged and an integrated approach is required for promoting self-care practices among diabetic patients to avert any long-term complications.[20]

Dietary management:

Dietary management involves controlling weight and the introduction of a healthy dieting plan. Healthy dieting is a critical component in the management of type 1 and type 2 diabetes. In over 50% of people presenting with type 2 diabetes retraction of energy intake, increased activity and weight reduction will initially normalize blood glucose, Diabetes Management in General Practice levels. Medication is likely to be needed later. While an appreciation of the dietary management of diabetes by the general practitioner or physician is important, detailed instructions need to be given by a dietitian.[21]

Nutrition therapy can reduce glycated hemoglobin by 1.0 to 2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes. Consistency in carbohydrate intake, and spacing and regularity in meal consumption may help control blood glucose and weight. Replacing high-glycemic index carbohydrates with low glycemic index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes.[22]

Physical activity:

Regular physical activity improves metabolic control and reduces other cardiovascular risks in people with diabetics. Low level aerobic exercise (e.g.: brisk walking for half an hour per day) and in the absence of contraindications, encourage performance of resistance training at least three times per week. Physical resistance training have the following benefits.[23]

- Improved glucose tolerance as insulin sensitivity increases
- Increased energy expenditure resulting in weight loss

- Increased feeling of well being
- Increased work capacity
- Improved blood pressure and lipid profiles.[21]

Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes.[24]

PHARMACOLOGIC MANAGEMENT

Anti-diabetic agent:

Multiple inventions and medications are needed to control the multiple risk factors associated with type 2 diabetes (hyper glycaemia, hypertension, dyslipidemia and increased thrombogenesis).[21]

There are six classes of oral agents are approved for the treatment of type 2 diabetes: α-glucosidase inhibitors, biguanides, meglitinides, peroxisome proliferator activated receptor β-agonists (Which are also commonly identified as thiazolidinediones or glitazones), sulfonylureas, incretin and gliptins. Oral agents are indicated for use in type 2 DM patients who are unable to achieve glycemic control goals despite diet and exercise. Oral antidiabetic agents are often grouped according to their glucose-lowering mechanism of action. Biguanides and thiazolidinediones are often categorized as insulin sensitizers due to their ability to reduce insulin resistance. sulfonylureas and meglitinides are often categorized as insulin secretagogues because they enhance endogenous insulin release.[9]

Sulfonyl ureas:

Sulfonylureas are classified as first-generation and second-generation agents. First-generation agents consist of acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Each of these agents is lower in potency relative to the second-generation drugs: glimepiride, glipizide, and glyburide. The primary mechanism of action of sulfonylureas is enhancement of insulin secretion. Sulfonylureas bind to a specific sulfonylurea receptor (SUR) on pancreatic β

cells. Binding closes an adenosine triphosphate – dependent K+ channel, leading to decreased potassium influx and subsequent depolarization of the membrane. Voltage-dependent Ca+2 channels open and allow and inward flux of Ca+2. Increases in intracellular Ca+2 cause translocation of secretory granules of insulin to the cell surface and resultant exocytosis of the granule of insulin. Elevated secretion of insulin from the pancreas travels via the portal vein and subsequently suppresses hepatic glucose production.[9]

All sulfonylureas are equally effective in lowering blood glucose when administered in equipotent doses. The recommended starting doses should be reduced in elderly patients who may have compromised renal or hepatic function. Dosage can be titrated every 1 to 2 weeks (longer interval with chlorpropamide) to achieve glycemic goals. On average, the HbA1c will fall by 1.5% to 2% with FPG reductions of 60 to 70 mg/dL. The most common side effect is hypoglycemia; Weight gain is common; less common adverse effects include skin rash, hemolytic anemia, gastrointestinal upset and cholestasis. Hyponatremia is most common with chlorpropamide but has also been reported with tolbutamide;[9]

Biguanides:

In most of the world, metformin is the only biguanides available. Its major effect is to decrease hepatic glucose output and lower fasting glycaemia.[25]Metformin enhances insulin sensitivity of both hepatic and peripheral (muscle) tissues. This allows for an increased uptake of glucose into these insulin-sensitive tissues. The exact mechanisms of how metformin accomplishes insulin sensitization are still being investigated, though adenosine 5'-monophosphate-activated protein kinase activity, tyrosine kinase activity enhancement, and glucose transporter 4 all play a part. Metformin has no direct effect on the β cells, though insulin levels are reduced, reflecting increases in insulin sensitivity.[9]

Clinical trials have documented that metformin therapy consistently decreases the fasting plasma glucose level by 3.3 to 3.9 mmol/L (60 to 70 mg/dL) and the HbA1c value by 1.5 to 2.0 percentage points in patients with poorly controlled diabetes.[26]

Metformin causes gastrointestinal side effects, including abdominal discomfort, stomach upset, and/or diarrhea in approximately 30% of patients. Anorexia and stomach fullness is likely part of the reason loss of weight is noted with metformin.[9]

Thiazolidines:

Thiazolidinediones are also referred to as TZDs or glitazones. Pioglitazone and rosiglitazone are the two currently approved thiazolidinediones for the treatment of type 2 DM. Thiazolidinediones work by binding to the peroxisome proliferator activator receptor-γ (PPAR-γ), which are primarily located on fact cells and vascular cells.[9] Like the sulfonylureas, theglinides stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor. Decreasing A1C levels by-1.5 percentage points. The risk of weight gain is similar to that for the sulfonylureas, but hypoglycemia may be less frequent.[25]

α-Glucosidase inhibitor:

α-Glucosidase inhibitors competitively inhibit enzymes (maltase, isomaltase, sucrose, and glucoamylase) in the small intestine, delaying the breakdown of sucrose and complex carbohydrates. They do not cause any malabsorption of these nutrients. The net effect from this action is to reduce the postprandial blood glucose rise.[9] Reducing A1C levels by 0.5 – 0.8 percentage points.[25]The gastrointestinal side effects, such as flatulence, bloating, abdominal discomfort, and diarrhea, are very common and greatly limit the use of α- glucosidase inhibitors.[9]

Insulin:

Insulin may be required if adequate control has not occurred on maximum does of hypoglycemic agents. However, ensure that exercise and dietary management are satisfactory and exacerbating factors e.g.: intercurrent infection, problems with medication has been excluded. Insulin may be needed early in the condition when treatment is being started (the so-called 'primary' failure of oral hypoglycemic agents that suggests the patient actually has type I

diabetes) or when the patient has later become refractory to oral hypoglycaemic agents (so-called 'secondary' failure consistent with the usual progression of type 2 diabetes). If the patient is symptomatic then insulin is required. If there are no symptoms but fasting blood glucose levels are consistently > 7.0 mmol/L, the decision is more difficult. When deciding glycaemic targets and considering insulin treatment, take into account: life expectancy, existing physical and psychosocial problems and potential problems with insulin. The selection of treatment goals, treatment schedules and monitoring schedules needs to be a decision arrived at after discussion with the patient and may be the stimulus for a General Practice Management Plan. Initiation of treatment with insulin is regarded as a major step by most patients. They require encouragement and psychological support. At this stage the help of a physician with a special interest in diabetes may useful. People with type 2 diabetes requiring insulin can often be managed with a singly daily dose of intermediate or long acting insulin added to their oral hypoglycaemic schedule.[21]

Incretin-Based Therapies:

Glucagon-like peptide-1(GLP-1):

Incretin mimetics are new class of antidiabetic agents first introduced in the years 2005 (exenatide) and liraglutide, respectively. Both use the antidiabetic properties of the incretin hormone, glucagon-like peptide (GLP)-1 a naturally occurring peptide produced by the L-cells of the small intestine, potentiates glucose-stimulated insulin secretion.[27]

When meals are consumed, the GI tract releases a number of hormones that aid in the absorption and disposition of nutrients. Among these, the hormones glucagon-like peptide-1

(GLP-1) and glucose-dependent insulinotropic peptide (GIP) are of particular importance because of their regulation of islet hormone secretion. GLP-1 and GIP augment glucose-stimulated insulin secretion, a process termed the incretin effect. The incretin effect account for approximately 50% of the insulin secreted after meals and therefore has a prominent role in postprandial metabolism. Incretin signaling is essential for normal glucose tolerance. In addition to stimulating insulin secretion; GLP-1 also inhibits glucagon secretion. Importantly, the incretin effect is impaired in subjects with T2DM, and this likely contributes to the abnormal control of

postmeal glucose levels that is a hall mark of this condition it decreases body weight and also inhibit the glucagon production.[28]

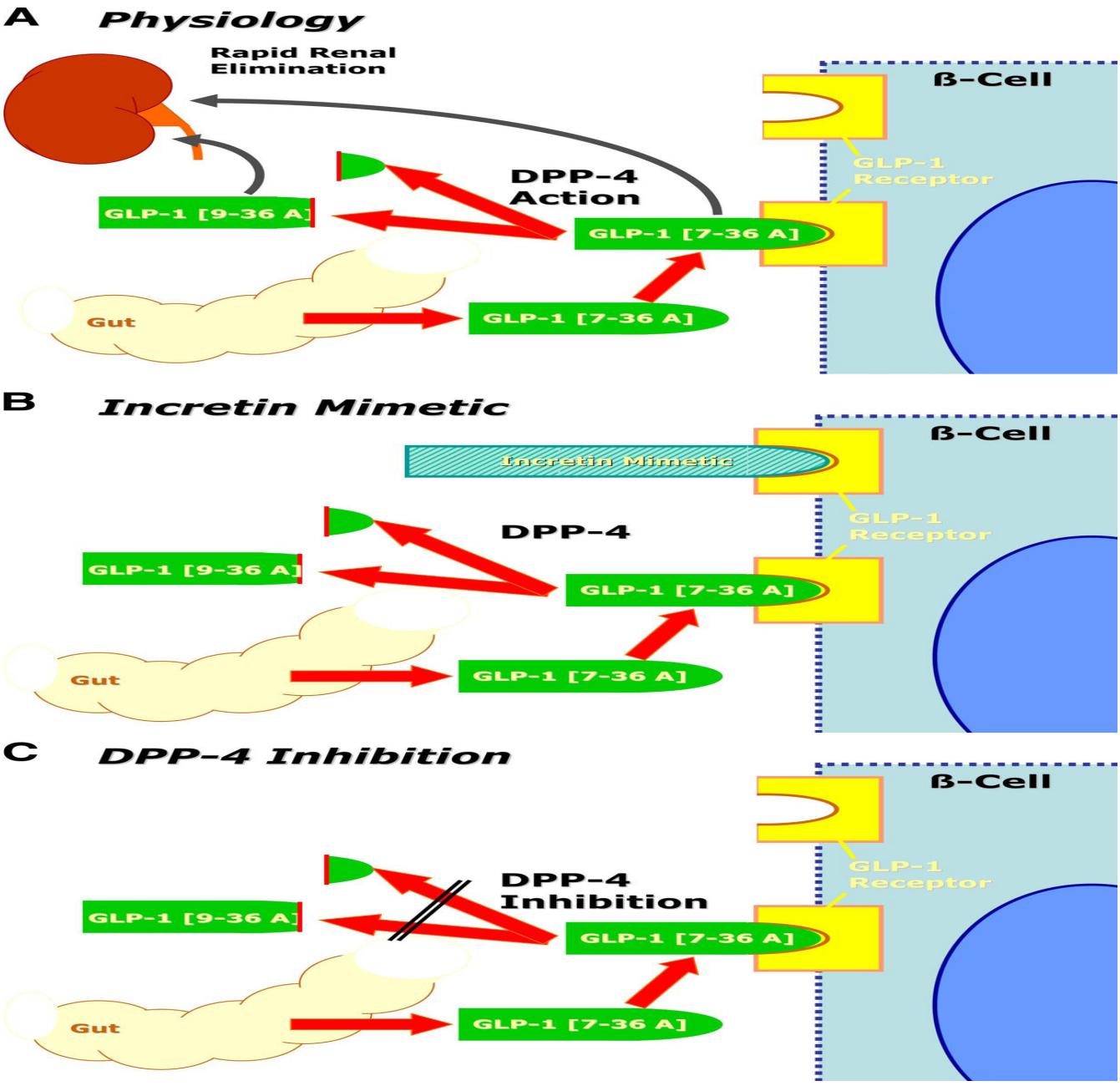


Figure 1- The Schematic diagram explaining the physiological (postprandial) secretion of GLP-1 from the gut, its binding to GLP-1 receptors (e.g., on pancreatic endocrine_-cells), and its degradation by the ubiquitous protease DPP-4 as well as its rapid renal elimination (A). Incretin mimetics are peptide GLP-1 receptor agonists more or less structurally similar to GLP-1, which bind and activate the GLP-1 receptor, but are not degraded by DPP-4 and have much slower elimination pharmacokinetics (B). DPP-4 inhibitors prevent the degradation/inactivation of the biologically active form of GLP-1 and, thereby, augment the biological activity of GLP-1 released from endogenous sources (C).[27]

Dipeptidyl peptidase four inhibitors. (DPP-4)

The DPP-4 inhibitors are the newest class of oral antihyperglycemic agents also commonly called gliptins. GLP-1 and glucose-dependent insulinotropic peptide (GIP), the main insulinotropic peptides of intestinal origin (incretins), are rapidly degraded by dipeptidyl peptidase four (DPP-4). DPP-4 is a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells. DPP-4 inhibitors are small molecules that enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion.[25]

The overall experience with DPP-4 inhibitions therefore that they are orally active, safe, and highly tolerable, with a minimal risk for hypoglycemic events. Furthermore, they show sustained, robust, and clinically significant improvement in glycemia in both monotherapy and combination with metformin and thiazolidinediones, and they are bodyweight neutral. The relevant mechanisms of action of DPP-4 inhibition (mainly improvement of islet function) and the efficacy, tolerability, and safety of treatment suggest that this approach has great potential as a novel treatment.

The clinical trials with gliptinshave measured fasting levels of lipids, and in general no or very little effects have been found on parameters such as cholesterol and triglycerides. This would suggest that DPP-4 inhibition does not affect lipid metabolism.

Results presented thus far suggest that DPP-4 inhibition has its strongest potential as a first-line treatment in early stages of type 2 diabetes in combination with metformin and thiazolidinediones. DPP-4 inhibitors are also strong candidates for being established as a first-line treatment as monotherapy, particularly in elderly subjects and in subjects with contraindication or intolerance for metformin or thiazolidinediones. DPP-4 inhibition may also

be used in combination with insulin with the great advantage of reducing the likelihood of developing hypoglycemia. Whether DPP-4 inhibition may also be advantageous over existing treatment in long term therapy of more advanced stages of the disease remains to be established.[29]

LITERATURE REVIEW

Maximilion von Eynatten, et al. (2013) in patients with type 2 diabetes mellitus (T2DM), hypertension and microalbinuria are predictive markers for increased renal and cardiovascular risk. This post hoc analysis of data from a global development program aimed to evaluate the efficacy and safety of Linagliptin in a population with joint prevalence of these two vascular risk factors. Data for patients with baseline micro albuminuria (urine albumin-to-creatinine ratio 30-300mg/g) and hypertension (systolic blood pressure≥140mm Hg and/or diastolic blood pressure≥90 mm Hg and /or a history of hypertension; and/or an antihypertensive treatment at baseline) who participated in any of six randomized, placebo-controlled, phase III trials were analyzed. Participants received Linagliptin 5mg daily (alone or in combination with other oral anti diabetic drugs) or placebo for 18 to 24 weeks. In T2DM patients with the two common vascular risk factors of hypertension and micro albuminuria, Linagliptin achieved significant improvements in glycemic control. In this vulnerable patient population at high risk for micro- and macro vascular complication, linagliptin was well tolerated.

Janet B. McGill, et al.(2013) the placebo- controlled study assessed long-termefficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in patients with type 2 diabetes and severe renal impairment(RI).In this 1-year,double blind study,133 patients with type 2 diabetes(HbA1c 7.0-10.0%) and severe RI (estimated glomerular filtration rate [eGFR] 30ml/min/1.73m^2) at screening were randomized to Linagliptin 5mg(n=68) or placebo(n=65) once daily, added to existing backround therapy. The primary efficacy end point was HbA1c change from baseline to week 12.Efficacy and safety end points were assessed after 1 year. In patients with type 2 diabetes and severe RI, Linagliptin provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug related renal failure. The potential for Linagliptin to spare insulin and provide long-term renal safety warrants further investigations.

Odd Erik Johansen, et al.(2012) this study investigated the cardiovascular safety profile of the dipeptidyl peptidase(DPP)-4 inhibitor Linagliptin versus comparator treatments. This was a pre-specified meta-analysis of CV events in Linagliptin or comparator-treated patients with type 2 diabetes mellitus (T2DM) from eight phase 3 studies. All suspected CV events were adjudicated by a blinded independent expert committee. The primary end point was a composite of CV death,

stroke, myocardial infarction, and hospitalization for unstable angina. Three secondary composite end points derived from the adjudicated CV events were also pre-specified. Risk estimates were calculated using several statistical methods including cox regression analysis. These results from a large phase 3 programme support the hypothesis that linagliptin may have CV benefits in patients with T2DM.

Debmalya sanyal, et al. (2013) new-onset diabetes after transplantation (NODAT) is frequently encountered after kidney transplant. In the present study, we retrospectively evaluated the safety and efficacy of Linagliptin monotherapy in 21 renal transplant recipients in a real world setting. We found Linagliptin monotherapy is effective for glycemic control in NODAT,even on glucocorticoids and standard dose of tacrolimus.There was no alteration of tacrolimus drug levels or estimated glomerular filtration rate and minimal side effects, including weight gain and hypoglycemia.well-designed,powered randomized controlled of antiglycemic agents in NODAT are needed.

Erica paniago guedes, et al. (2013) linagliptin: farmacology, efficacy and safety in the type 2 diabetes treatment. Type 2 diabetes patients have dysfunction in incretin hormones (as glucagon-like peptide-1 or GLP-1 and glucose-dependent insulinotropic polypeptide or GIP).By inhibiting the dipeptidyl pepdidase-4(DPP-4) enzyme; it is possible to slow the inactivation of GLP-1 and GIP, promoting blood glucose level reduction in a glucose-dependent manner. Linagliptin is a highly specific and potent inhibitor of DPP-4 that is currently indicated for the treatment of type2 diabetes. Clinical studies with Linagliptin demonstrated efficacy in reducing glycated haemoglobin (HbA1c) levels in type 2 diabetes patients, while maintaining a placebo-like safety and tolerability profile. Linagliptin has an interesting pharmacokinetic profile in terms of its predominantly non-renal elimination and the main implication of this characteristic is that no dose adjustment is necessary in patients with renal disease. Also, no dose adjustment is required in patients with hepatic insufficiency, as well in elderly or obese patients. This article will review the pharmacokinetic profile, efficacy data and safety aspects of Linagliptin in type 2 diabetes patients.

Hannele Yki-jarvinen, et al. (2013) evaluates the effects of adding Linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes. A total of 1,261 patients (HbA1c≥7.0%[53mmol/mol]to≤10.0%[86mmol/mol])on basal insulin alone or combined with metformin and/or pioglitazone were randomized(1:1)to double-blind treatment with Linagliptin 5mg once daily or placebo for≥52 weeks. The basal insulin dose was kept unchanged for 24 weeks but could thereafter be titrated according to fasting plasma glucose levels at the investigators discretion. The primary end point was the mean change inHbA1c from baseline to week 24.the safety analysis incorporated data up to a maximum of 110 weeks. Linagliptin added to basal insulin therapy significantly improved glycemic control relative to placebo without increasing hypoglycemia or body weight.

Barry J.Goldstein, et al. (2007) assess the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes and inadequate glycemic control on diet and exercise. In a 24-week,randomized,double-blind,placebo-controlled,parallel-group study,1091 patients with type 2 diabetes and HbA1c 7.5-11% were randomized to one of six daily to the treatment:sitagliptin100mg/metformin1000mg(S100/M1000group),sitagliptin 100mg/metformin2,000mg (S100/M2000 group),metformin1000mg(M1000 group),metformin 2,000mg(M2000 group)(all as divided doses administered twice daily [b.i.d]) sitagliptin100mg q.d (S100 group),or placebo. Patients who had an HbA1c >11% or a fasting glucose value>280mg/dl after the run- in period were not eligible to be randomized; these patients could participate in an open-label sub study and were treated with S100/M2000 for 24 weeks. The initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with type 2 diabetes.

Carolina Solis-Herrera, et al.(2013) assess mechanism of glucose lowering of sitagliptin(S),metformin(M) and two combined (M+S) in type 2 diabetes. We randomized 16 patients with type 2 diabetes mellitus(T2DM) to four 6-week treatments with placebo(P),M,S,andM+S.After each period, subjects received a 6-h meal tolerance test(MTT) with[^{14} C]glucose to calculate glucose kinetics. Fasting plasma glucose (FPG), fasting plasma insulin, C-peptide (insulin secretory rate [ISR]), fasting plasma glucagon, and bioactive glucagon-like peptide (GLP-1) and gastrointestinal insulinotropic peptide (GIP) were measured.M+S combined produce additive effects to; reduce FPG and post meal glucose,

augment GLP-1 secretion and b-cell function, decrease plasma glucagon, and inhibit fasting and post meal EGP compared with M or S monotherapy.

Guillermo E. Umpierrez, et al. (2013) this study investigated the safety and efficacy of sitagliptin (Januvia) for the inpatient management of type 2 diabetes (T2D) in general medicine and surgery patients. In this pilot, multicenter, open-label, randomized study, patients (n=90) with a known history of T2D treated with diet, oral anti diabetic agents, or low total daily dose of insulin (≤0.4 units/kg/day) were randomized to receive sitagliptin alone or in combination with glargine insulin (glargine) or to a basal bolus insulin regimen (glargine and lispro) plus supplemental (correction) doses of lispro. Major study outcomes included differences in daily blood glucose (BG), frequency of treatment failures (defined as three or more consecutive BG>240mg/dl or a mean daily BG>240mg/dl), and hypoglycemia between groups. Results of this pilot indicate that treatment with sitagliptin alone or in combination with basal insulin is safe and effective for the management of hyperglycemia in general medicine and surgery patients with T2D.

Jorge Luiz Gross, et al. (2013) A novel model- based meta-analysis to indirectly estimate the comparative efficacy of two medication: an example using DPP-4 inhibitors, sitagliptin and linagliptin,in treatment of type 2 diabetes mellitus.

Kaustubh Nisal,et al. (2012) type 2 diabetes mellitus is widely prevalent and is often coexistent with obesity. Many of the available treatment options have side effects such as weight gain which often affect patient's willingness to continue the treatment. Effective weight loss, lack of significant hypoglycaemia, and favorable cardiometabolic profile make incretin based therapies an attractive treatment option for type 2 diabetes. Incretin based therapies are available as either incretin mimetics(also called GLP-1 agonists)or incretin enhancers (DPP-4 inhibitors).Although agents in both these classes of incretin based therapy are effective through a common GLP-1 pathway, there are many differences amongst them including the route of administration, frequency of administration, effects on body weight, extent of glycaemic improvement. There are several trials evaluating these individual incretin based agents either as monotherapy or in combination with other anti-diabetic agents, however very few have looked into direct comparison amongst the agents in these two classes. This review is aimed to look at important mechanistic differences between incretin mimetics and enhancers through direct comparison

trials and impact of these differences on biochemical, metabolic and patient satisfaction parameters.

Masaya Sakamoto,et al.(2012) assess the comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring(CGM).twenty patients with type 2 diabetes mellitus were randomly allocated to groups who received vildagliptin then sitagliptin, or vice versa. Patients were hospitalized at 1 month after starting each drug, and CGM was used to determine: mean(±standard deviation) 24-hour blood glucose level, mean amplitude of glycemic excursions(MAGE),fasting blood glucose level, highest post prandial blood glucose level and time, increase in blood glucose level after each meal, area under the curve(AUC) for blood glucose level≥180mg/dl within 3 hours after each meal, area over the curve(AOC) for daily blood glucose level<70mg/dl,plasma glycosylated hemoglobin(HbA1c),glycoalbumin(GA),1,5-anhydroglucitol(1,5AG),immunoreactive insulin(IRI),C-peptide immunoreactivity(CPR),brain natriuretic peptide(BNP),and plasminogen activator inhibitor-1(PAI-1) levels, and urinary CPR levels, were measured.CGM showed that mean 24-h blood glucose,MAGE,highest blood glucose level after supper, and hyperglycemia after breakfast were significantly lower in patients with type 2 diabetes mellitus taking vildagliptin than those taking sitagliptin. There were no significant differences in BNP and PAI-1 levels between patients taking vildagliptin and sitagliptin.

Roger Gadsby, et al.(2009) review the efficacy and safety of sitagliptin and discuss its place in therapy.Evidance from a Cochrane review and meta-analysis of 14 trials or study arms suggests that sitagliptin lowers HbA1c by0.7% in sitagliptin versus placebo trials. Evidence from a pooled safety database of 3415 people taking sitagliptin, and the Cochrane review show that the drug is well tolerated, causes no hypoglycemia and is weight neutral. No specific signals of concern for the safety of sitagliptin have so far arusen in the pooled database. Guidelines recommended its use in triple therapy with metformin and sulphonylurea in dual therapy with metformin or sulphonylurea or thiazolidinedione in certain cercumstances.sitagliptin from this initial data appears to be a safe, weight neutral and effective anti-diabetic agent.

Akira Kanamori, et al. (2013) this study (as part of ASSET-K) aimed to investigate the efficacy and safety of sitagliptin when it was administered for 1.5 years or longer, and to explore factors associated with reduction of the therapeutic response. Out of 375 patients treated with sitagliptin (50mg/day) at kanamori diabetes clinic between December 2009 and March2012, 133 could be followed up for 72 weeks without interruption. After excluding 40 patients in whom the dosage and/or types of concomitant medications were modified during that period, the remaining 93 were included in this analysis. Clinical indices, such as blood glucose, HbA1c, and body weight, were investigated respectively. Compliance with diet and exercise therapy at 48 weeks was checked by a questionnaire. Sitagliptin showed good efficacy and safety when administered for 18 months as both monotherapy and combination therapy. Inadequate compliance with diet/exercise therapy and weight gain may be associated with an increase of HbA1c over time during treatment with sitagliptin.

EleFerrannini, et al. (2013) investigate the long-term safety and efficacy of empagliflozin, sitagliptin and metformin in patients with type 2 diabetes.in this randomized, open label,78-week extension study of two 12-week,blinded,dose-finding studies of empagliflozin(monotherapy and add-on to metformin) with open-label comparators,272 patients received 10mg empagliflozin(166 as add-on to metformin), 275 received 25 mg empagliflozin(166 as add-on to metformin),56 patients received metformin, and 56 patients received sitagliptin as add-on to metformin. Long-term empagliflozin treatment provided sustained glycemic and weight control and was well tolerated with a low risk of hypoglycemia in patients with type 2 diabetes.

GuntramSchernthaner, et al. (2013) evaluate the efficacy and safety of canagliflozin,a sodium glucose cotransporter 2 inhibitor, compared with sitagliptin in subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea. In this 52-week, randomized, double-blind, active-controlled, phase 3 study, subjects using stable metformin plus sulfonylurea (N=755) received canagliflozin 300 mg or sitagliptin 100mg daily. Primary end point was change from baseline in A1C at 52 weeks. Secondary end points included change in fasting plasma glucose (FPG) and systolic blood pressure (BP), and percent change in body weight, triglycerides, and HDL cholesterol, Safety was assessed based on adverse event (AE) reports. Findings suggest that canagliflozin may be a new therapeutic tool providing better improvement

in glycemic control and body weight reduction than sitagliptin, but with increased genital infections in subjects with type 2 diabetes using metformin plus sulfonylurea.

Ralph A.Defronzo, et al. (2009) this 24-week trial assessed the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes with inadequate glycemic control with metformin alone. This was a randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, or 10mg once daily) or placebo plus a stable dose of metformin (1500-2500 mg) in 743 patients (A1c≥7.0 and ≤ 10.0%).Efficacy analyses were performed using an ANCOVA model using last observation carried forward methodology on primary (A1c) and secondary (fasting plasma glucose [FPG] and postprandial glucose [PPG] area under the curve [AUC]) end points. Saxagliptin once daily added to metformin therapy was generally well tolerated and led to statistically significant improvements in glycemic indexes versus placebo added to metformin in patients with type 2 diabetes inadequately controlled with metformin alone.

Muthukrishnanjayaraman, et al. (2013) there reports of acute pancreatitis with the use of dipeptidyl peptidase-4 inhibitors (gliptins).This class of drugs is widely being prescribed for type 2 diabetes mellitus (DM) in our country. We evaluated the incidence of acute pancreatitis with the use of gliptins during the period January 2012-june 2013.patients of type 2 DM on treatment with any of the gliptins (sitagliptin, vildagliptin, or saxagliptin) for at least 1 month duration were included. A total of 185 patients were included (205.3 patient years of follow-up).Five of them had history of acute pancreatitis (all mild) >6 months prior to inclusion with complete resolution and no chronic pancreatitis. One patient (0.48 per 100 patient years) presented with mild acute pancreatitis which resolved in 8 days. Asymptomatic elevation of serum amylase > 3x upper limit of normal was noted in five patients (2.4 per 100 patient years), without any sonological evidence of pancreatitis. This resolved on withdrawal of gliptins. None of the patients with previous history of pancreatitis had a recurrence of pancreatitis. In a group at low risk of acute pancreatitis, incidence of acute pancreatitis is low with the use of gliptins.

Robert Frederich, et al.(2012) the aim of this study was to assess efficacy and safety of saxagliptin monotherapy for up to &76 weeks in patients with type 2 diabetes mellitus (T2DM) and inadequate glycemic control, with main efficacy assessment at 24 weeks.365 treatment-naïve patients with T2DM(HbA1c 7.0-10.0%) were treated with saxagliptin 2.5 mg q.A.M, saxagliptin

2.5 mg q.A.M with possible titration to saxagliptin 5 mg, saxagliptin 5mg q.A.M,saxagliptin 5 mg q.P.M,or placebo, After week 24,patients in all groups were eligible for titration to saxagliptin 10 mg based on HbA1c ≥7%, and all unrescued placebo patients began blinded metformin 500 mg/day. Rescue with open-label metformin was available for patients with inadequate glycemic control. In treatment-naïve patients with T2DM, saxagliptin monotherapy demonstrated statistically significant improvement in HbA1c compared with placebo at 24 weeks and generally well tolerated for up to 76 weeks.

Iftekar H, et al. (2012) type 2 diabetes mellitus (T2DM) is epidemic in most developing countries and is a leading cause of morbidity and mortality. Vildagliptin represent a new class of oral anti-diabetic agent that enhance the action of incretin hormone through inhibition of dipeptidylpeptidase-4.The enhancement of incretin hormone(GLP-1 & GIP) potentiates the insulin secretion in β-cells and suppress the glucagon release by α-cells in the pancreas. The present article reviews the impact of DPP-4 inhibitor, Vildagliptin in monotherapy as well as combination with a special emphasis on the Risk & Benefits on different organs of T2DM patients. Vildagliptin is a potent & specific DPP-4 inhibitor that has demonstrated weigh neutrally, and improves β-cell as well as cardiovascular function in patient with DM type 2 in multiple monotherapy & combination. However, hypoglycemic event reported with combination of metformin, rosiglitazone and SU, but safe with pioglitazone, while in combination with insulin the event was found to be reduced. Vildagliptin also shows feedback inhibition of GLP-1 secretion which reduces risk of cardiovascular and hypoglycemia, where as it concern to increasing the risk of pancreatitis according to post marketing surveillance.

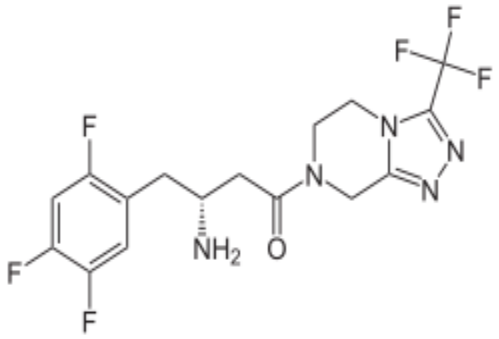
DRUG PROFILE

SITAGLIPTIN[50, 51]

DESCRIPTION:

Sitagliptin is a new oral hypoglycemic (anti-diabetic drug) of the new dipeptidyl peptidase4 (DPP-4) Inhibitor class of drugs. Previously identified as MK-0431 and marketed as the phosphate salt under the trade name Januvia. It was developed, and is marketed, by Merck & Co. This enzyme-inhibiting drug is to be used either alone or in combination with Metformin or a thiazolidinedione for control of type 2 diabetes mellitus. The drug works to competitively inhibit a protein / enzyme, dipeptidylpeptidase4 (DPP-4), that results in an increased amount of active incretins (GLP-1 and GIP), reduced amount of release of glucagon (diminishes its release) and increased release of insulin.

STRUCTURE:



®-4-0xo-4-[3- (trifluoromethyl)-5, 6diydro[1,2,4] triazolo [4,3-a]pyrazin-7 (8H)-yl]-1-(2,4,5-trifluoropenyl) butan-2-amine.

Molecular weight =Average: 407.3136g/mol

Molecular formula=$C_{16}H_{15}F_5N_5O$

MECHANISM OF ACTION:

Sitagliptin is a highly selective DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, thereby increasing the concentration and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal.

These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion form pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose dependent manner. These changes lead to a decrease in hemoglobin A1C (HbA1c) levels, as well as a lower fasting and postprandial glucose concentration. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

INDICATION:

Adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus as monotherapy or as combination therapy.

PHARMACOKINETICS:

Absorption

Sitagliptin is rapidly absorbed, with a 100mg does reaching a Cmax of 950nM in 1 to 4h; AUC was 8.52 mcM. The bioavailability is approximately 87%

Distribution

Vd is approximately 198 L.Plasma protein binding is 38%

Metabolism

Metabolism by CYP3A4 and, to a lesser degree, CYP2C8

Elimination

Terminal half-life is approximately 12.4h and renal clearance is approximately 350ml/min.Approximately 13% excreted in the feces and 87% in the urine via active tubular secretion (79% as unchanged drug). Sitagliptin is substrate for organic anion transport.

PHARMACODYNAMIC:

Sitagliptin is an orally-active member of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. The benefit of this medicine is expected to be its lower side-effects of hypoglycemia in the control of blood glucose values. The drug works to diminish the effects of a protein/enzyme (by the inhibition of this protein/enzyme) on the pancreas at the level of release of glucagon (diminishes its release) and at the level of insulin (increases its synthesis and release) until blood glucose levels are restored toward normal, in which case the protein/enzyme inhibitor becomes less effective and the amounts of insulin released diminishes thus diminishing the "overshoot" of hypoglycemia seen in other oral hypoglycemic agents.

DOSE AND ADMINISTRATION:

Adult

PO 100mg once daily

Adults moderate renal impairment (crc130 to less than 50ml/min or approximate serum creatinine levels of more than 1.7 up to 3mg/dl in men and more than 1.5 up to 2.5mg/dl in women).

PO 50mg once daily

Severe renal impairment (Crcl less than 30ml/min or approximate serum creatinine levels of more than 3mg/dl in men and more than 2.5mg/dl in women).

PO 25mg once daily

Administer without regard the timing of hemodialysis.

CONTRAINDICATION:

History of serious hypersensitivity reaction to sitagliptin.

DRUG INTERACTION:

Cyclosporine

Sitagliptin plasma concentration may be increased modestly (approximately 68%), wich is not expected to be clinically important.

Digoxin

Digoxin concentration may be increased slightly (approximately 18%), no dosage adjustment is recommended.

Insulin, sulfonylureas (eg: tolbutamide)

ADVERSE DRUG REACTION:

GI

Diarrhea (3%). abdominal pain (2%) nausea (1%); post marketing report pancreatitis.

Respiratory

Nasopharyngitis, upper respiratory tract infection (5%)

Miscellaneous

Headache(1%), hypoglycemia.

PRECAUTION:

Periodically monitor blood glucose and HbA1c. Assess renal function prior to initiation of therapy and periodically thereafter. Observe patients carefully for signs and symptoms of pancreatitis.

STORAGE AND STABILITY:

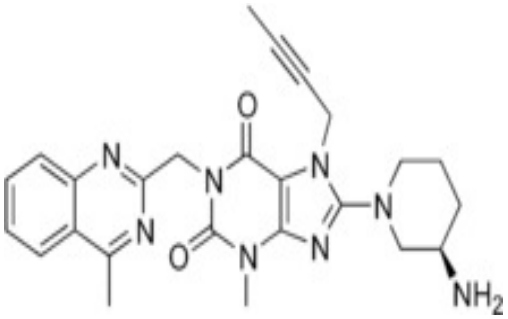
Store at 59° to 86° F

LINAGLIPTIN[50, 51]

DESCRIPTION:

Linagliptin (BI-1356, trade name Tradjenta and Trajenta) is a DPP-4 inhibitor developed by Boehringer ingelheim for treatment of type II diabetes. Linagliptin (once daily) was approved by the food and drug administration (FDA) on 2011 and is being marketed by Boehringer ingelheim and Lilly.

STRUCTURE:



8-[(3R)-3-aminopiperidin-1yl]-7-(but-2yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2yl) methyl]-3, 7dihydro-1-H-purine-2, 6-dione

Molecular weight =472.54g/mol

Molecular formula= $C_{25}H_{28}N_8O_2$

MECHANISM OF ACTION:

Linagliptin is a competitive and reversible dipeptidyl peptidase (DPP)-4 enzyme inhibitor that slows the breakdown of insulinotropic hormone glucagon-like peptide (GLP)-1 for better glycemic control in diabetes patients. GLP and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones that increase the production and release of insulin from pancreatic beta cells and decrease the release of glucagon from pancreatic alpha cells. This results in an overall decrease in glucose production in the liver and increase an of insulin in a glucose dependent manner.

INDICATION:

Linagliptin is used for the management of type 2 diabetes mellitus.

PHRAMACOKINETICS:

Absorption

Cmax, 5mg, healthy subjects=8.32nmol/L; Tmax, 5mg, healthy subjects =1.75 hours; AUC (0-24 hours), 5mgn, healthy subjects=119 nmol h/L; Bioavailability, healthy subjects=30%. When a dose of 5mg once daily is given, steady state is achieved by the third dose. Although a high fat meal reduces Cmax and increase AUC, this interaction with food is not clinically significant. Linagliptin may be administered with or without food.

Distribution

Vd=1110L, 70-80% protein bound.

Metabolism

Linagliptin is not extensively metabolized, 90% of does is excreted unchanged. The small portion of drug that is metabolized, the main metabolite is CD1790 and is pharmacologically inactive. Glucuronidation forms some.

Elimination

Linagliptin is eliminated via the faces/ enterohepatic system (80%) and urine (5%). This is unlike other DPP-4 inhibitors which are primarily eliminated by the renal system. Terminal half-life=131 hours. Because of this long half-life, inhibition of DPP-4 activity is sustained which indicates that once-daily dosing is appropriate. Effective half-life for accumulation of drug is 12 hours when multiple. Renal clearance, steady state=mL/min.

PHARMACODYNAMICS:

Linagliptin is more potent inhibitor of DPP-4 than other drugs that belongs to the same class with an IC50 of 1 nM. In comparison, sitagliptin, saxagliptin, and vildagliptin have an IC50 of 19, 50, and 62nM respectively. A dose of 2.5 and 5mg reduces the activity of DPP-4 by 72.7% and 86.1% from respectively in healthy male subjects. In diabetes patients, a dose of 5 and 10mg inhibits >90% of DPP-4. Linagliptin is also selectively inhibits DPP-4 as indicated by the lack of DPP-8 or DPP-9 inhibition at therapeutic exposures in vitro.

DOSE AND ADMINISTRATION:

Adult

PO 5mg once daily.

CONTRANDICATION:

Produce history of serious hypersensitivity reaction for linagliptin.

DRUG INTERACTION:

Carbamazepine:	CYP3A4 and p-glycoprotein inducers may decreases levels of linagliptin. Monitor concomitant therapy closely.
Etravirine:	Linagliptin, when used concomitantly with etravirine (a strong CYP3A4 Inducer, may experience a decrease in serum concentration; It is recommended to avoid concurrent therapy if possible, and to monitor Linagliptin therapy if concurrent cannot be avoided.
Hydrocortisone:	CYP3A4 inducers may decrease levels of Linagliptin and diminish the hypoglycemic effect of anti-diabetic agents.
Prednisone:	CYP3A4 inducers may decrease level of Linagliptin and diminish the hypoglycemic effect of anti-diabetic agents.

Rifampin: CYP3A4 and p-glycoprotein inducers may decreases levels of Linagliptin.
Ritonavir: CYP3A4 inhibitors may increase levels of linagliptin.

ADVERSE DRUG REACTION:

Nasopharyngitis, Rash, hypoglycemia,

PRECAUTION:

When used with an insulin secretagogue (e.g. Sulfonylurea) or with insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

The use of Linagliptin with insulin was associated with a higher rate of hypoglycemia in patients with severe renal impairment and a lower dose of insulin may be required.

Safety and effectiveness have not been established in pediatric patients (less than 18 years of age).

WARNINGS:

Linagliptin has been assigned to pregnancy category B by the FDA.

There are no data on the excretion of Linagliptin into human milk. The manufacturer recommends that caution be used when administering linagliptin to nursing women.

STORAGE

Store at room temperature away from moisture and heat.

AIM AND OBJECTIVE

AIM:

The aim of the present study was to compare the efficacy and safety of linagliptin with that of sitagliptin among type 2 diabetic patients".

OBJECTIVE:

- To assess the comparative efficacy of the DPP-4 inhibitors linagliptin/sitagliptin through, Fasting plasma glucose (FPG), post prandial glucose (PPG) and glycated haemoglobin (HbA1c) levels along with lipid profile and BMI measure in a period of 6 months.
- To evaluate and compare the safety of the linagliptin/sitagliptin drugs by following the assessment of renal profile, hepatic profile (Liver Function Test).

PLAN OF WORK

The present dissertation work was planned to conduct a **"comparative study on efficacy and safety of linagliptin vs. sitagliptin drugs in the treatment of type 2 diabetes mellitus"**. And was planned to conduct in Annamalai diabetic research center at Karaikudi.

The plan of work includes:

1. Submission of the protocol for getting the approval from ethical committee.
2. To get consent letter from patient.
3. To design a data collection form.
4. To collect the case histories of the patient with type2 diabetes.
5. To divide the patient into two groups randomly.
6. Fasting blood glucose (FPG), post prandial glucose (PPG), glycated haemoglobin (HbA1c), body mass index (BMI), Lipid profile, Renal profile, Hepatic profile values are measure at baseline and end of the study.
7. To evaluate collected data.
8. Carrying out statistical analysis and recorded.

MATERIALS AND METHODS

STUDY DESIGN:

This study is aProspective observational study.

STUDY SETTING:

The study was carried out on type 2 diabetic patients visiting the outpatient department in Annamalai diabetic care and research center, Karaikudi**.**It is one of the reputed Hospital in karaikudi.Majority of patients come from the surrounding rural areas.

SOURCE OF DATA:

The required data was collected by using data collection form.

POPULATION SIZE:

A total 100 patients were enrolled for the study. The patients were randomly divided into 2 groups, In which 50 patients each were group A (linagliptin 5 mg) and group B (sitagliptin 100 mg).

STUDY CRITERIA:

Inclusion criteria:

- Glycosylated haemoglobin>7%
- Patients of age between 30-70 years.
- Type 2 diabetic patients.

Exclusion criteria:

- Type 1 diabetic patient.
- Diabetic ketoacidosis
- Patient with renal and hepatic dysfunction.
- Pregnant lactating women.

STUDY PERIOD:

Study was conducted for a period of 6 months.

(September 2013 to February 2014)

ETHICAL APPROVAL:

The institutional human ethical committee of MGR university approved the study.

INFORMED CONSENT:

A suitably prepared consent form was used for the purpose of the study.

METHODOLOGY

STATISTICAL ANALYSIS:

Data analysis was done with help of computer using Instat package(version 0.36, 2003)

DATACOLLECTION:

- Those patients receive linagliptin, sitagliptin were introduced in group A and group B.
- The patients were given instruction to monitor their blood glucose level, HbA1c, lipid profile, renal profile, and hepatic profile (Liver Function Test) at the initial visit to hospital.
- The patient records were maintained for the next six month after their initial visit to hospital.
- The patients were observed for weight, height and BMI measurement.
- The records of age, sex and other possible associated diseases were also maintained.
- The patients were asked for the determination of blood glucose level,HbA1c, lipid profile, renal profile, and hepatic profile (LFT) .regularly at the interval of 3 months up to end of the study .

PRIMARY PARAMETER	**SECONDARY PARAMETER**
1. Fasting glucose level:	**Lipid profile**
2. PPG:	1.TC, TGL
3. HbA1c value:	2.LDL
4. BMI value:	3.HDL

RENAL SAFETY	**HEPATIC SAFETY**
1. Serum creatinine:	1.Total bilirubin:
2. Uric acid:	2. ALT/ SGPT:
3. Urea:	3. AST/ SGOT:

OBSERVATION AND RESULTS

The work entitled **"comparison on efficacy and safety of Linagliptin Vs. sitagliptin among type 2 diabetic patients"**. Was carried out in Annamalai Diabetic research centre, Karaikudi.A total of 100 patients were randomized to include in this study. There patients were distributed into two groups such as Group A on Linagliptin. Group B on Sitagliptin.

All patients baseline parameters were recorded before the treatment as initial values and recorded at each follow up. Also values of all parameters were recorded after 6 month and compared the values.

The information collected recording all the selected cases were recorded in a master chart. Data analysis was done with the help of computer using **Instat package (version 3.06, 2003).**

Using this software means, standard deviations, 'p' values were calculated. Paired t test was used to test the significance of difference between quantitative variables and qualitative variables.A'p' value less than 0.05 is taken to denote significant relationship.

PATIENT DEMOGRAPHY

Table 1: Age distribution

AGE	GROUP A		GROUP B		TOTAL NO OF PATIENTS
	NO OF PATIENTS	PERCENTAGE (%)	NO OF PATIENTS	PERCENTAGE (%)	
40 to 50 YEARS	23	46	23	46	46
51 to 60 YEARS	27	54	27	54	54
TOTAL	50		50		100

Out of 100 patients, 50 patients were Group A, from these 23 patients (46%) were age between 40-50 years, and 27 patients (54%) were age between 51-60 years.

Out of 100 patients, 50 patients were Group B, from these 23 patients (46%) were age between 40-50 years, and 27 patients (54%) were age between 51-60 years.

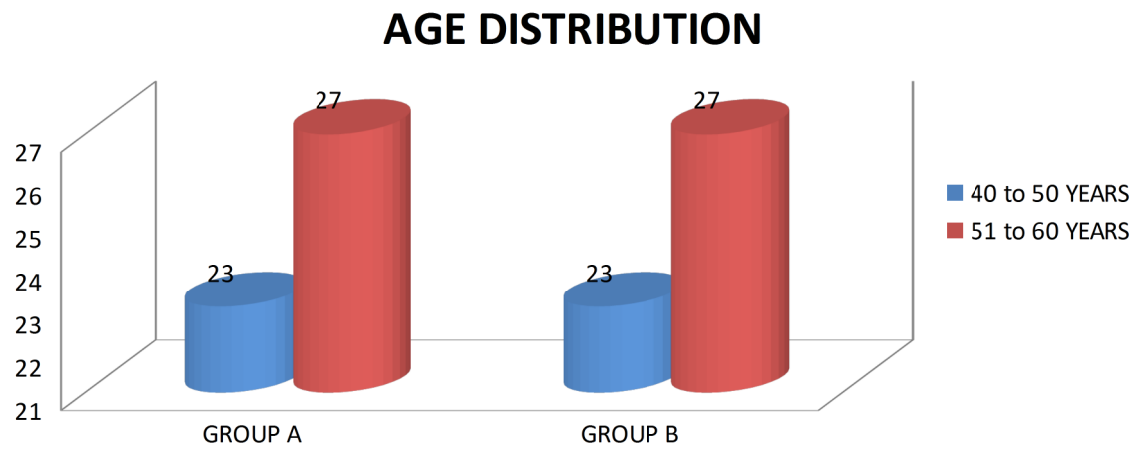


FIGURE: 1

Table 2: Sex distribution

SEX	GROUP A		GROUP B		TOTAL NO OF PATIENTS
	NO OF PATIENTS	PERCENTAGE (%)	NO OF PATIENTS	PERCENTAGE (%)	
MALE	26	52	26	52	52
FEMALE	24	48	24	48	48
TOTAL	50		50		100

A total of 100 patients were screened and randomized into two treatment groups. Out of 50 on Group A, from these 26 patients (52%) were male and 24 patients (48%) were female.

Out of 50 on Group B, from these 26 patients (52%) were male and 24 patients (48%) were female.

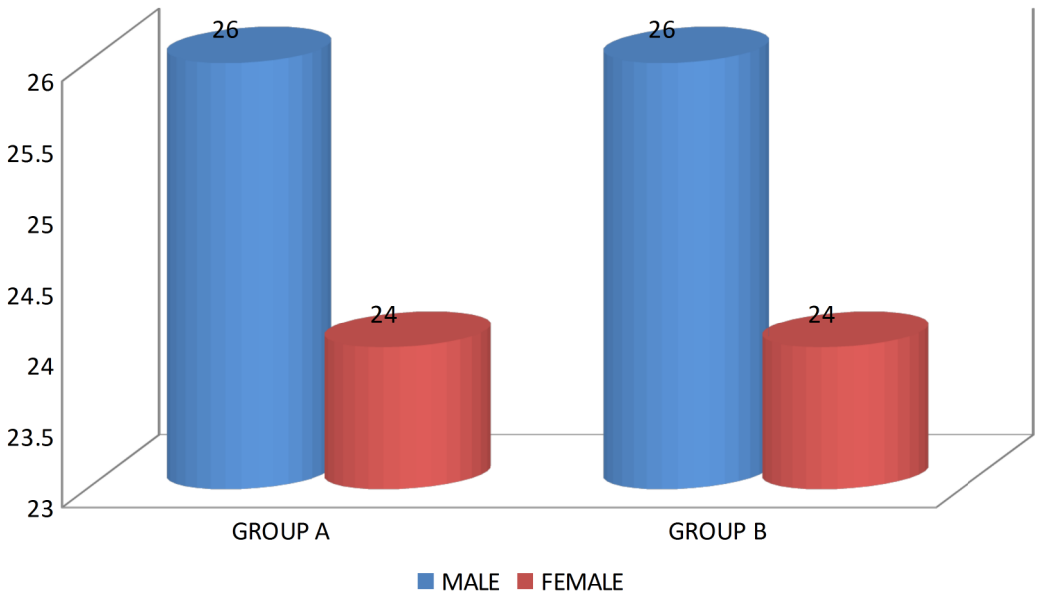


FIGURE: 2

Table 3: Duration of DM

DURATION OF DM (IN YEARS)	GROUP A		GROUP B	
	NO OF PATIENTS	PERCENTAGE (%)	NO OF PATIENTS	PERCENTAGE (%)
0 TO 3 YEARS	11	22	14	28
4 TO 7 YEARS	34	68	33	66
ABOVE 7 YEARS	5	10	3	6
TOTAL	50		50	

Out Of 100 patients, 50 patients were Group A, from these 11 patients (22%) duration of DM were between 0-3 years, 34 patients (68%) duration of DM were 4-7 years, and 5 patients (10%) duration of DM were above 7 years.

Another 50 patients were Group B, from these 14 patients (28%) duration of DM were between 0-3 years, 33 patients (66%) duration of DM were 4-7 years, and 3 patients (6%) duration of DM were above 7 years.

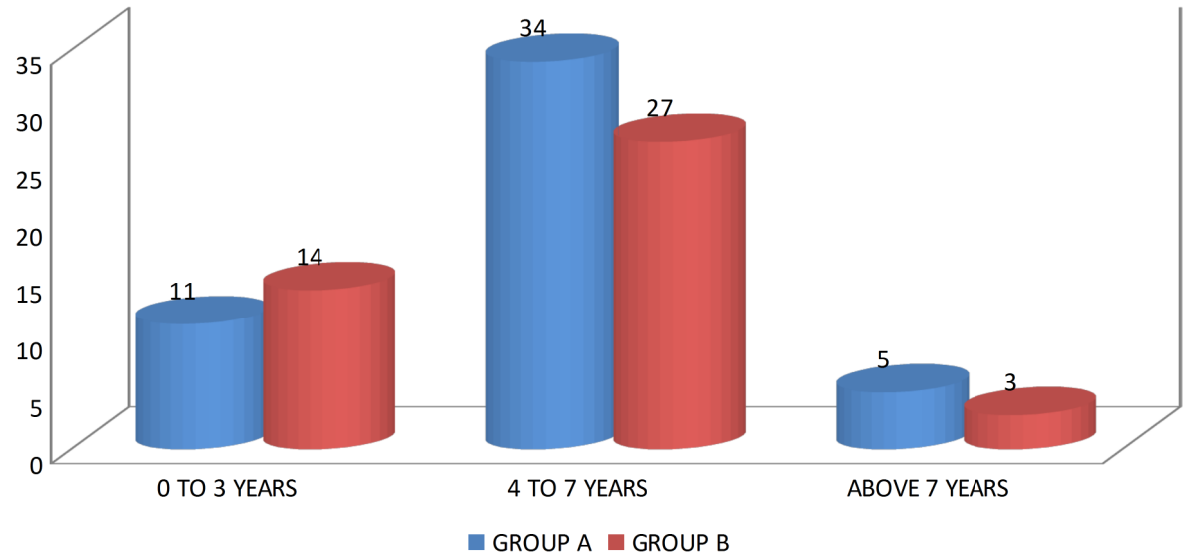


FIGURE: 3

EFFICACY MEASUREMENT

Table 4: Fasting plasma glucose value

PATIENTS VISIT TO HOSPITAL	FASTING PLASMA GLUCOSE VALUE IN MEAN ±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
FIRST VISIT	132.1±19.32	130.8±19.95	0.6902 Not significant
SECOND VISIT	105.2±3.4	114.8±8.7	0.0001 Significant
THIRD VISIT	100.2±12.3	112.1±13.9	0.0001 Significant
MEAN CHANGE IN SECOND VISIT	26.9±15.9	16±11.2	0.0001 Significant
MEAN CHANGE IN THIRD VISIT	31.9±7.02	18.7±6.05	0.0001 Significant

The fasting plasma glucose values were had significance reduction in two groups. The reduction of fasting plasma glucose, group A was greater than that in the group B.

Order of reduction =Group A > Group B

The P value of fasting plasma glucose after second and third visit were 0.0001, which was significant.P value of decreasing blood sugar after second and third visit were 0.0001, which was also significant.

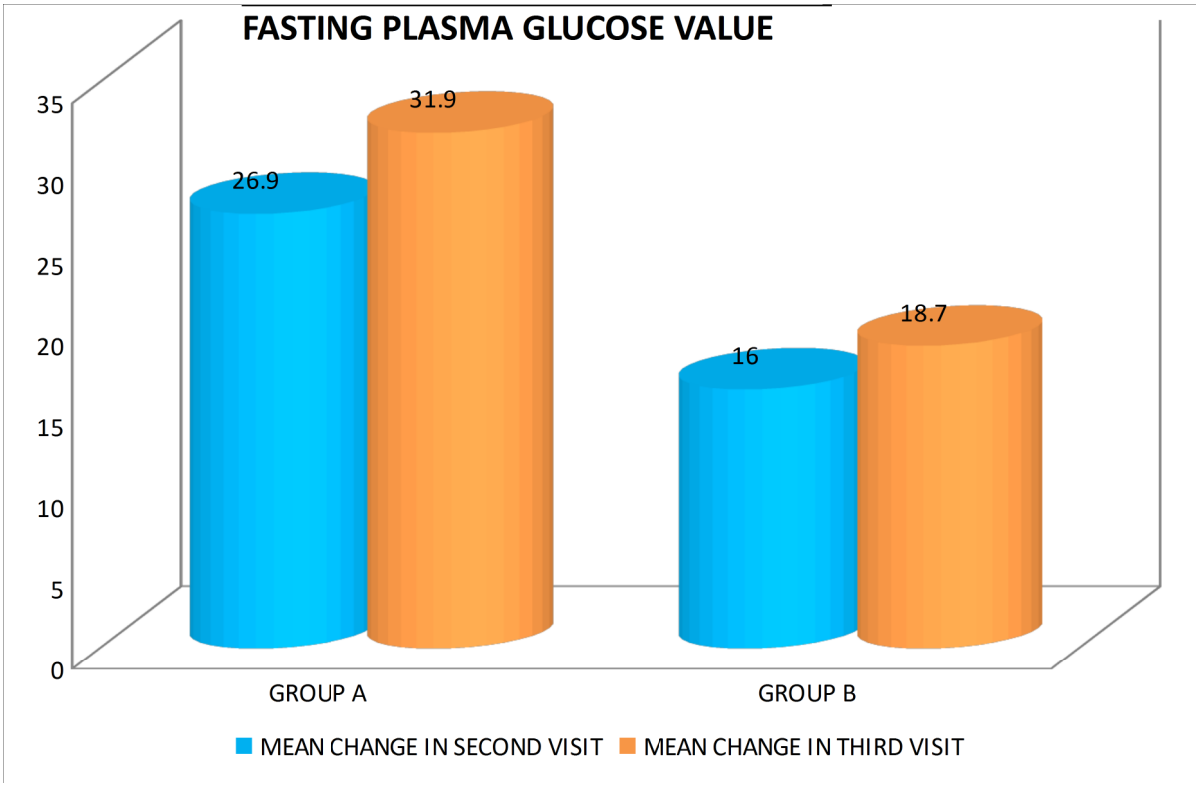


FIGURE: 4

Table 5: Post prandial plasma glucose value

PATIENT VISIT TO HOSPITAL	POST PRANDIAL PLASMA GLUCOSE VALUE AT MEAN ±SD(Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
FIRST VISIT	221.6±18.9	217.7±26.4	0.3847 Not significant
SECOND VISIT	138.6±16.3	168.1±14.6	0.0001

			significant
THIRD VISIT	136.6±16.1	149.5±11.7	0.0001 Significant
MEAN CHANGE IN SECOND VISIT	83±2.6	49.6±11.8	0.0001 Significant
MEAN CHANGE IN THIRD VISIT	85±2.8	68.2±14.7	0.0001 Significant

The post prandial plasma glucose values were had significance reduction in two groups. The reduction of fasting plasma glucose, group A was greater than that of group B.

Order of reduction =Group A > Group B

The P value of post prandial plasma glucose after second and third visit were 0.0001, which was significant.P value of decreasing post prandial after second and third visit were 0.0001, which was also significant.

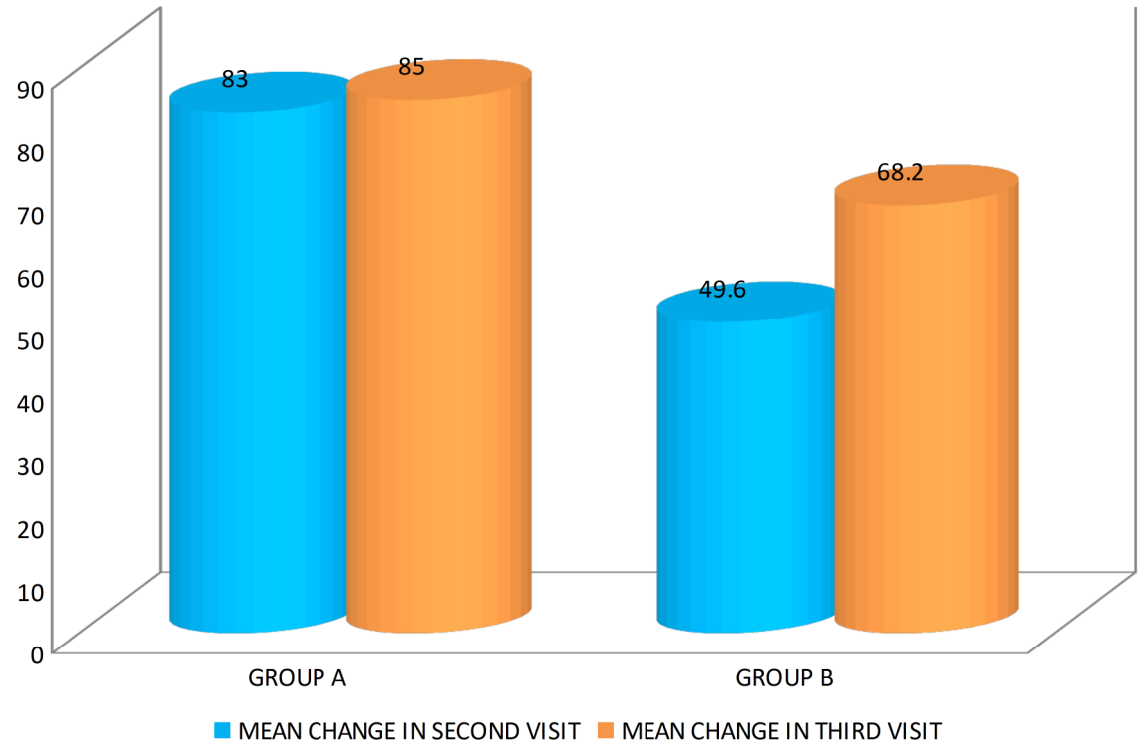


FIGURE: 5

Table 6: HbA1c value

PATIENTS VISIT TO HOSPITAL	HbA1c VALUE IN MEAN ±SD (%)		'P' VALUE
	GROUP A	GROUP B	
FIRST VISIT		7.7±0.4	0.7906

	7.7±0.3		Not significant
SECOND VISIT	6.6±0.5	7.3±0.48	0.0001 significant
THIRD VISIT	6.5±0.4	6.9±0.5	0.0001 Significant
MEAN CHANGE IN SECOND VISIT	1.1±0.2	0.4±0.08	0.0001 significant
MEAN CHANGE IN THIRD VISIT	1.2±0.1	0.8±0.1	0.0001 significant

The HbA1c levels were found to be reduced significance in patients with two groups.

The group Ashowed greater reduction in HbA1c after third visit.

Order of reduction in HbA1c = Group A > Group B

The P value of HbA1c after third visit was 0.0001, which was significant.

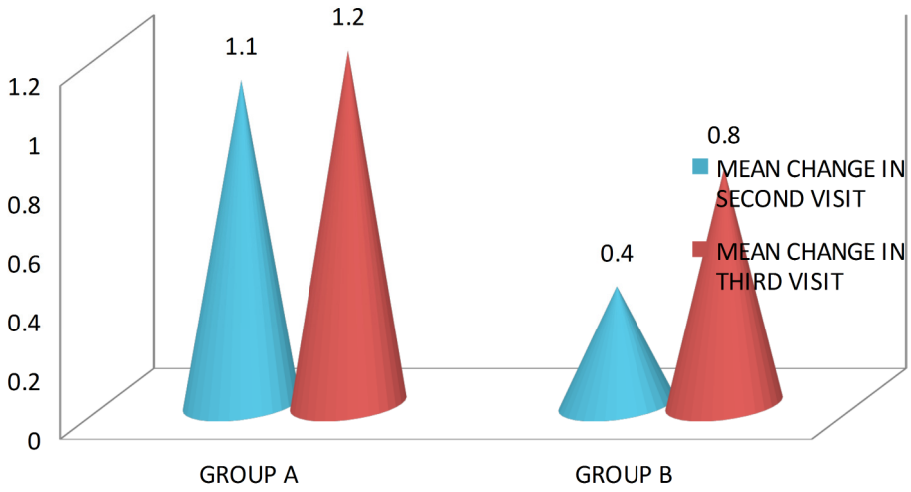


FIGURE: 6

Table 7: Body mass index value

	BMI (Kg/m^2)	'P' VALUE

PATIENTS VISIT TO HOSPITAL	GROUP A	GROUP B	
FIRST VISIT	25.93±1.15	25.83±1.15	0.6647 Not significant
THIRD VISIT	25.92±1.13	25.85±1.0	0.7436 Not significant
BMI CHANGE IN THIRD VISIT	0.01±0.02	0.02±0.15	0.6413 Not significant

The BMI levels were found to be not significance in patients with group A and group B. The P value of BMI after third visit was 0.7436, which was not statistically significant. The P value of BMI change after third visit was 0.6413, which was also not significant.

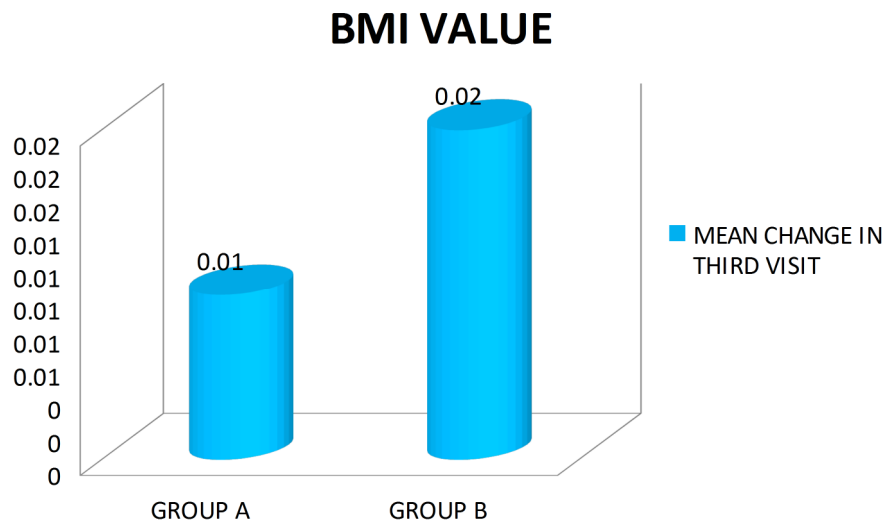


FIGURE: 7

SECONDARY PARAMETER

LIPID PROFILE

Table 8: Total cholesterol value

PATIENT VISIT TO HOSPITAL	TOTAL CHOLESTEROL VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	TC	TC	
FIRST VISIT	168.6±12.8	169.7±11.8	0.6683 Not significant
SECOND VISIT	167.22±23.14	168.84±17.29	0.6955 Not Significant
THIRD VISIT	166.12±22.71	168.38±19.39	0.5648 Not Significant
MEAN CHANGE IN SECOND VISIT	1.38±10.34	0.86±5.49	0.7543 Not significant
MEAN CHANGE IN THIRD VISIT	2.48±9.91	1.32±7.59	0.5128 Not significant

The mean total cholesterol level were had not significance reduction in two groups. The mean change of total cholesterol, group A was high than that of group B.

Order of reduction= Group A > Group B

The P values of total cholesterol after second and third visit were 0.6955, 0.5648 which was not significant.P values of total cholesterol mean change in after second and third visit were 0.7543,0.5128 which was also not significant.

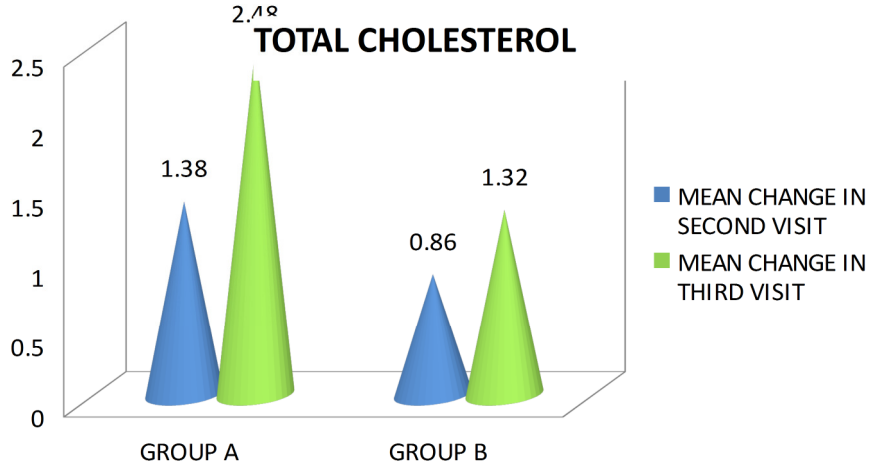


FIGURE: 8

Table 9: Triglycerides value

PATIENT VISIT TO HOSPITAL	TRIGLYCERIDES VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	TGL	TGL	
FIRST VISIT	137±14.2	139.9±12.9	0.2267 Not significant
SECOND VISIT	134.72±13.57	138.84±13.19	0.0889 Not significant
THIRD VISIT	131.2±18.82	136.64±14.95	0.0766 Not significant
MEAN CHANGE IN SECOND VISIT	2.28±0.63	1.06±0.29	0.0001 significant
MEAN CHANGE IN THIRD VISIT	5.8±4.62	3.26±2.05	0.0007 significant

The mean triglycerides levels were had not significance reduction in two groups. The mean change of triglycerides, group A was high than that of group B.

Order of reduction= Group A > Group B

The P values of triglycerides after second and third visit were 0.0889, 0.0766 which was a not significant.P value of triglycerides mean change in after second and third visit were 0.0001, 0.0007 which was significant.

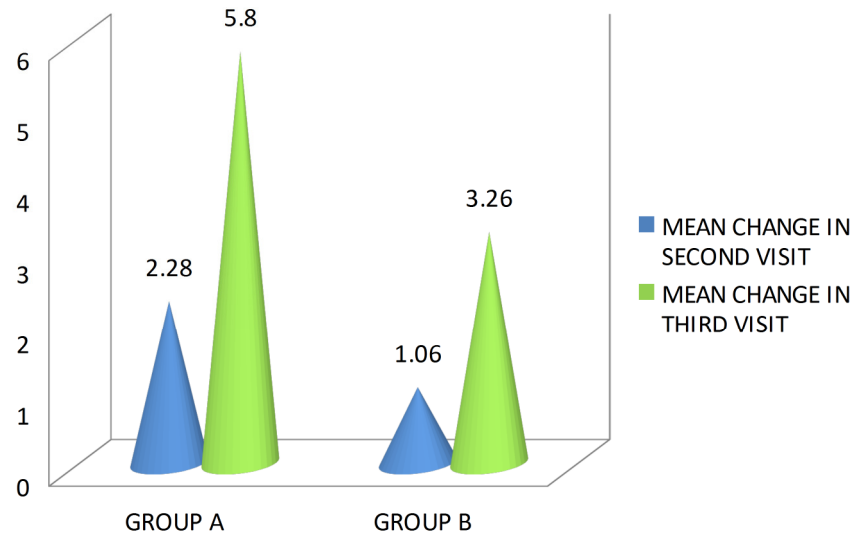


FIGURE: 9

Table 10: Low density lipid value

PATIENT VISIT TO HOSPITAL	LOW DENSITY LIPID VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	LDL	LDL	
FIRST VISIT	96±12.7	99.3±15.9	0.1747 Not significant
SECOND VISIT	94.3±17.0	97.96±17.44	0.3093 Not Significant
THIRD VISIT	91.74±20.27	96.18±18.52	0.2482 Not Significant
MEAN CHANGE IN SECOND VISIT	1.7±4.3	1.34±1.54	0.5793 Not Significant
MEAN CHANGE IN THIRD VISIT	4.26±7.57	3.12±2.62	0.3183 Not significant

The mean low density lipid levels were had not significance reduction in two groups. The mean change of low density lipid level, group A was high than that of group B.

Order of reduction= Group A > Group B

The P values of low density lipid after secondand third visit were 0.3093, 0.2482, which was not significant.P values of low density lipid mean change in after second and third visit were 0.5793,0.3183 which was also not significant.

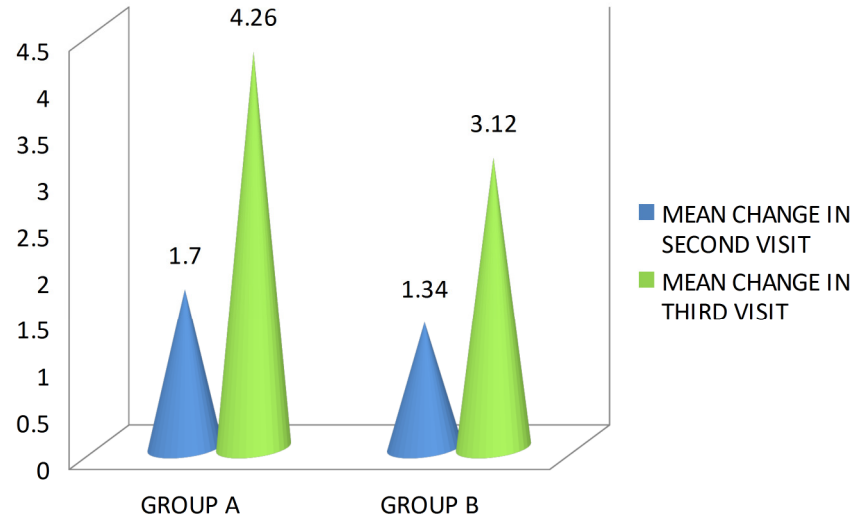


FIGURE: 10

Table 11: High density lipid value

PATIENT VISIT TO HOSPITAL	HIGH DENSITY LIPID VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	HDL	HDL	
FIRST VISIT	37.3±4.5	35.7±3.7	0.0742 Not significant
SECOND VISIT	40.2±4.3	36.9±5.1	0.0003 Significant
THIRD VISIT	43.4±3.9	38.4±8.7	0.0001 Significant
MEAN CHANGE IN SECOND VISIT	2.9±0.2	1.2±1.4	0.0001 Significant
MEAN CHANGE IN THIRD VISIT	6.1±0.6	2.7±5.0	0.0001 Significant

The mean high density lipid levels were had significant increase in two groups. The mean change of high density lipid, group A was greater than that of group B.

Order of increase = Group A > Group B

The P values of high density lipid after visit 0.0003 and third visit were 0.0001, which was significant.P values of high density lipid mean change in after second and third visit were 0.0001, which was also significant.

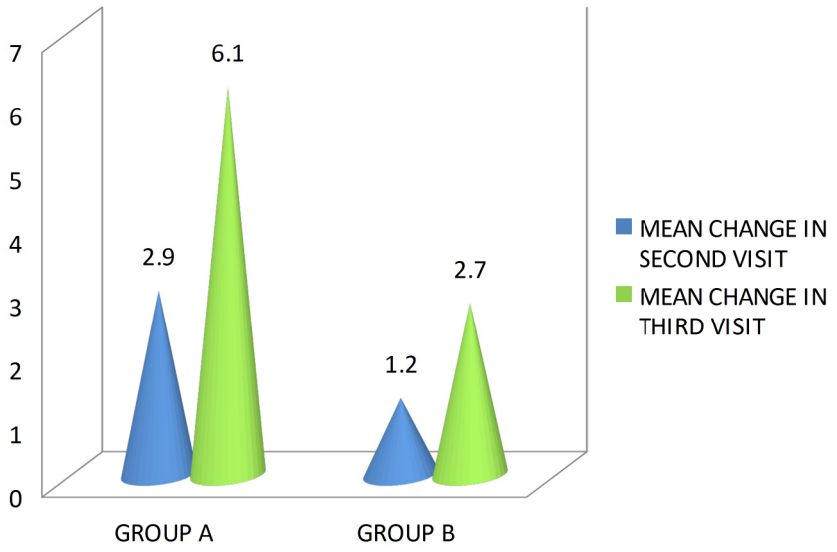


FIGURE: 11

SAFETY MEASUREMENT

RENAL PROFILE

Table 12: Serum creatinine value

PATIENT VISIT TO HOSPITAL	SERUM CREATININE VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	SR CR	SR CR	
FIRST VISIT	0.97±0.05	0.98±0.04	0.8372 Not significant
SECOND VISIT	0.96±0.09	0.97±0.06	0.5453 Not significant
THIRD VISIT	0.98±0.09	1.00±0.07	0.1824 Not significant
MEAN CHANGE IN SECOND VISIT	0.01±0.04	0.01±0.02	0.9999 Not significant
MEAN CHANGE IN THIRD VISIT	0.01±0.04	0.02±0.03	0.1605 Not significant

The patients mean values of serum creatinine showed changes slightly but not significance in group A and group B.The P value of serum creatinine after second visit 0.5453 and third visit was 0.1824, which was not statistically significant. The P value of serum creatinine mean change second and third visit respectively 0.9999, 0.1605, which was also not significant.

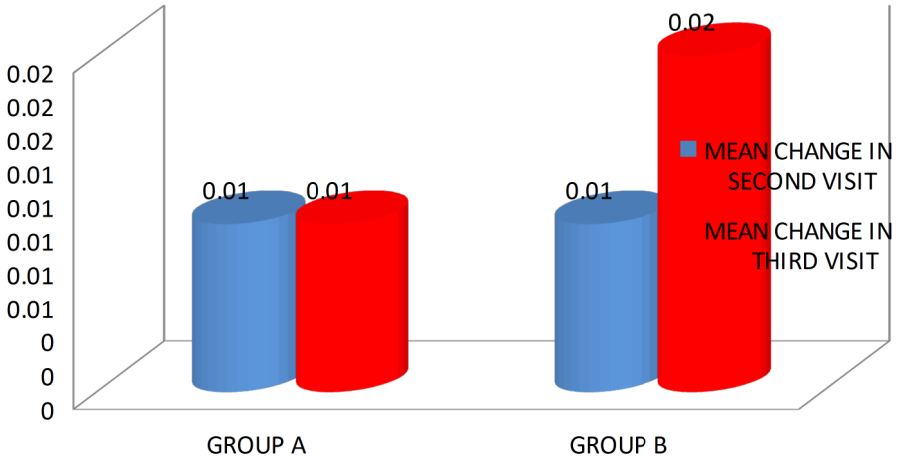


FIGURE: 12

Table 13: Blood urea value

PATIENT VISIT TO HOSPITAL	BLOOD UREA VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	B U	B U	
FIRST VISIT	27.66±3.28	27.78±3.20	0.8457 Not significant
SECOND VISIT	27.56±3.58	27.76±3.55	0.7541 Not significant
THIRD VISIT	27.62±3.1	27.84±3.5	0.7452 Not significant
MEAN CHANGE IN SECOND VISIT	0.1±0.3	0.02±0.35	0.2227 Not significant
MEAN CHANGE IN THIRD VISIT	0.04±0.1	0.06±0.3	0.6557 Not significant

The patients mean values of blood urea showed changes slightly but not significance in group A and group B.The P value of blood urea after second visit 0.7541 and third visit was 0.7452, which was not statistically significant. The P values of blood urea mean changes in second and third visit respectively 0.2227, 0.6557, which was also not significant.

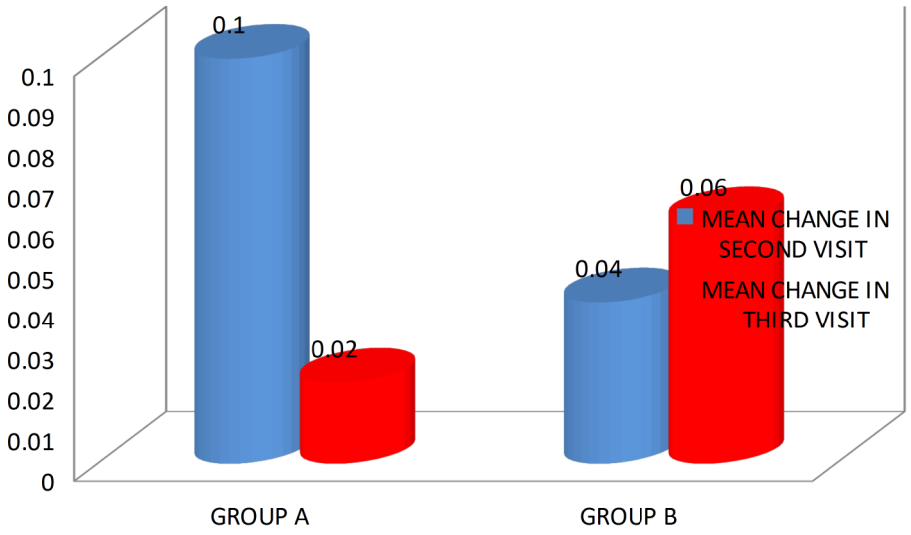


FIGURE: 13

Table 14: serum uric acid value

PATIENT VISIT TO HOSPITAL	SERUM URIC ACID VALUE IN MEAN±SD (Mg/dl)		'P' VALUE
	GROUP A	GROUP B	
	SUA	SUA	
FIRST VISIT	4.36±0.7	4.47±0.62	0.3669 Not significant
SECOND VISIT	4.40±0.6	4.41±0.66	0.9293 Not significant
THIRD VISIT	4.37±0.6	4.49±0.63	0.3033 Not significant
MEAN CHANGE IN SECOND VISIT	0.04±0.1	0.06±0.04	0.1922 Not significant
MEAN CHANGE IN THIRD VISIT	0.01±0.1	0.02±0.01	0.4834 Not significant

The patients mean values of serum uric acid showed changes slightly but not significance in group A and group B.The P value of serum uric acid after second visit 0.9293 and third visit was 0.3033, which was not statistically significant. The P values of serum uric acid mean change in second and third visit respectively 0.1922, 0.0.4834, which was also not significant.

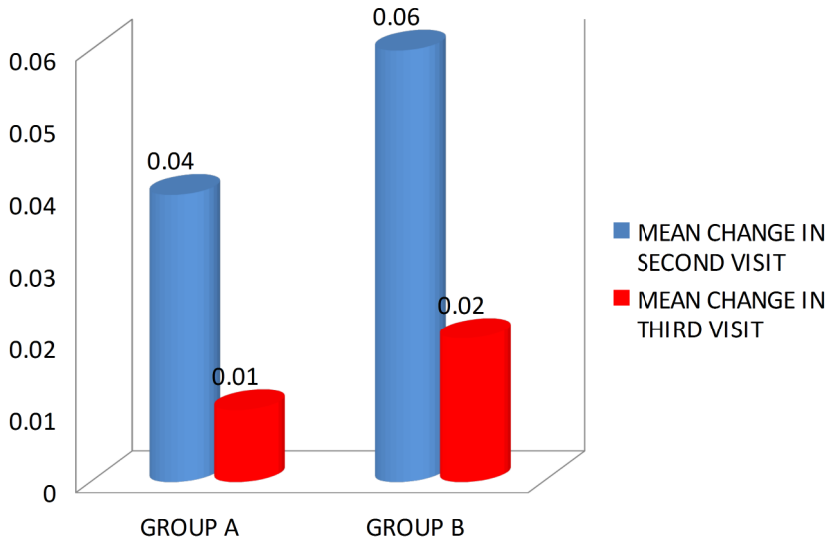


FIGURE: 14

HEPATIC PROFILE (LIVER FUNCTION TEST)

Table 15: Total bilirubin value

PATIENT VISIT TO HOSPITAL	TOTAL BILIRUBIN VALUE IN MEAN±SD (Mmol/L)		'P' VALUE
	GROUP A	GROUP B	
	T B	TB	
FIRST VISIT	0.95±0.05	0.95±0.06	0.9999 Not significant
SECOND VISIT	0.94±0.06	0.96±0.07	0.0673 Not significant
THIRD VISIT	0.96±0.06	0.94±0.07	0.3414 Not significant
MEAN CHANGE IN SECOND VISIT	0.01±0.01	0.01±0.01	0.9999 Not significant
MEAN CHANGE IN THIRD VISIT	0.01±0.01	0.01±0.01	0.9999 Not significant

The patients mean values of total bilirubin showed changes slightly but not significance in group A and group B.The P value of total bilirubin after second visit 0.0673 and third visit was 0.3414, which was not statistically significant. The P values of total bilirubin mean changes in second and third visit respectively 0.9999, 0.9999, which was also not significant.

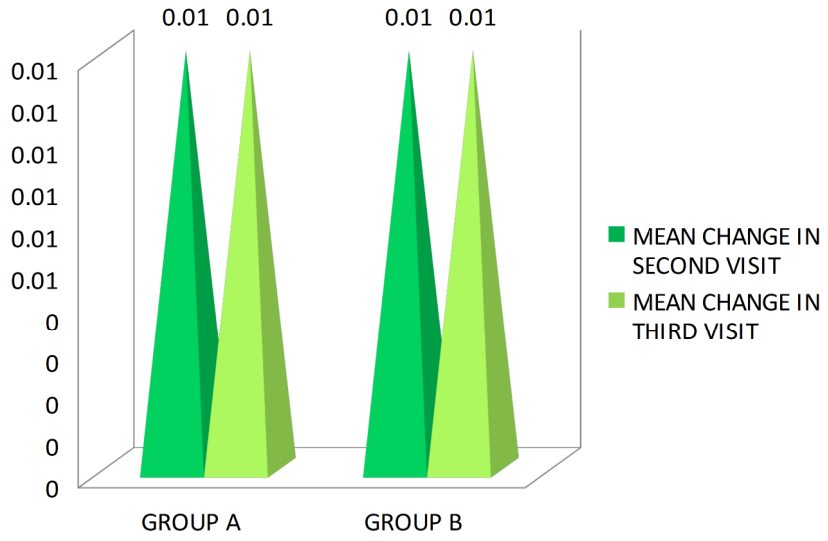


FIGURE: 15

Table 16: SGOT/ALT values

PATIENT VISIT TO HOSPITAL	SGOT/ALT VALUE IN MEAN±SD (U/L)		'P' VALUE
	GROUP A	GROUP B	
	SGOT/ALT	SGOT/ALT	
FIRST VISIT	28.82±4.2	29.02±4.74	0.8228 Not significant
SECOND VISIT	28.42±4.27	29.54±3.92	0.1846 Not significant
THIRD VISIT	28.76±5	29.1±4.9	0.6958 Not significant
MEAN CHANGE IN SECOND VISIT	0.4±0.07	0.52±0.82	0.3807 Not significant
MEAN CHANGE IN THIRD VISIT	0.04±0.08	0.08±0.16	0.1171 Not significant

The patients mean values of SGOT/ALT showed changes slightly but not significance in group A and group B.The P value of SGOT/ALT after second visit 0.1846 and third visit was 0.6958, which was not statistically significant. The P values of serum creatinine mean changes in second and third visit respectively 0.3807, 0.1171, which was also not significant.

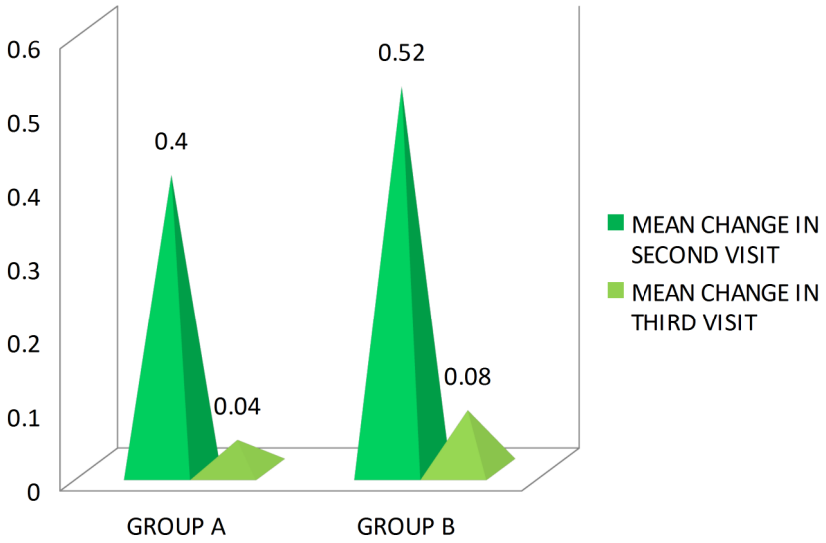


FIGURE: 16

Table 17: SGPT/AST values

PATIENT VISIT TO HOSPITAL	SGPT/AST VALUE IN MEAN±SD (U/L)		'P' VALUE
	GROUP A	GROUP B	
	SGPT/AST	SGPT/AST	
FIRST VISIT	29.1±4.2	29.6±3.9	0.4541 Not significant
SECOND VISIT	28.9±6.1	30.0±4.5	0.3180 Not significant
THIRD VISIT	29.2±5.1	29.7±3.8	0.6313 Not significant
MEAN CHANGE IN SECOND VISIT	0.2±1.9	0.4±0.6	0.4795 Not significant
MEAN CHANGE IN THIRD VISIT	0.1±0.9	0.1±0.1	0.9999 Not significant

The patients mean values of SGPT/AST showed changes slightly but not significance in group A and group B.The P value of SGPT/AST after second visit 0.3180 and third visit was 0.6313, which was not statistically significant. The P values of SGPT/AST mean changes in second and third visit respectively 0.4795, 0.9999, which was also not significant.

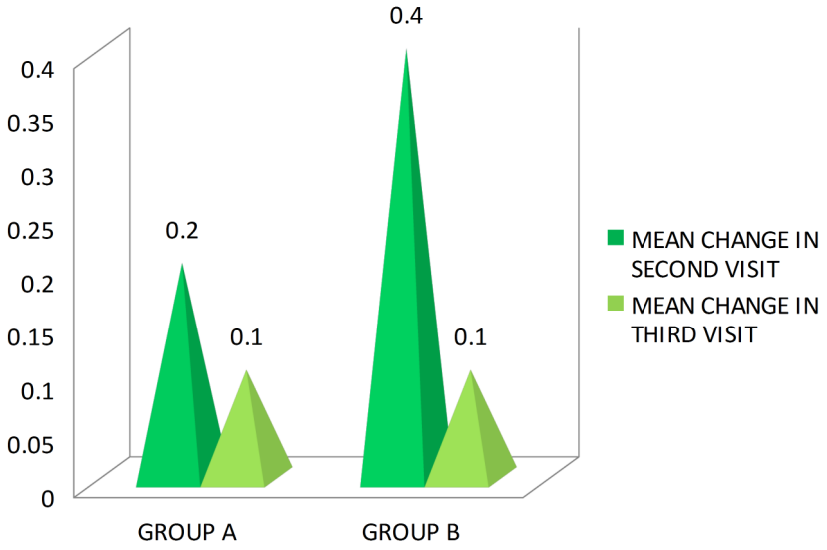

0.4
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0.2
0.1
0.1
GROUP A
GROUP B
MEAN CHANGE IN SECOND VISIT
MEAN CHANGE IN THIRD VISIT

FIGURE: 17

DISCUSSION

The results of this prospective observational study suggest that in patient with type 2 diabetes mellitus. Our study is the first to our knowledge, to investigate the efficacy and safety of linagliptin vs. sitagliptin among type 2 diabetes mellitus.

- A total of 100 patients, 50 patients were Group A, from these 46% were age between 40-50 years, and 54% were age between 51-60 years, in which 52% were male and 48% were female. Remaining 50 patients were Group B, from these 46% were age between 40-50 years, and 54% were age between 51-60 years, in which 52% were male and 48% were female.
- Out Of 100 patients, 50 patients were Group A, from these 22% patients duration of DM were between 0-3 years,68% patients duration of DM were 4-7 years, and10% patients duration of DM were above 7 years. Another 50 patients were Group B, from these 28% patients duration of DM were between 0-3 years,66% patients duration of DM were 4-7 years, and 6% patients duration of DM were above 7 years.
- In this post hoc analysis of patients with T2DM showed significant and clinically relevant reductions in fasting blood sugar, post prandial blood sugar, HbA1c level in group A and group B, in which group A had greater reduction than group B.
- The BMI values of group A and group B had slight changes but P value of the both group A and B were statistically not significant. That indicated weight should not be changed.

- The mean values of lipid profile were total cholesterol, LDL had reduced from baseline at second and third visit on both group A and group B, but which was not significant on mean and mean changes. Even though numerically group A have high reduction than group B. The mean values of triglycerides shown not significance at second and third visit on both group A&B, but mean changes of second and third visit were statistically

significant. The mean and mean change values of HDL were significantly increased from baseline at second and third visit on both group A and group B, in which group A greater than group B.

- The mean values of renal profile group A and group B were serum creatinine, blood urea, serum uric acid had tiny changes but P values of the both groups were statistically not significant.
- The mean values of hepatic profile(LFT) group A and group B were total bilirubin, SGOT/ALT, SGPT/AST had tiny changes but P values of the both groups were statistically not significant.

Preventing or delaying the development of type 2 diabetes is major goals of treatment. Our finding indicates that this goal can be achieved if high risk of patients are identified early in the course of disease and are in the given appropriate therapy. However, renal and hepatic impairment can be a limiting factor in the selection of antihyperglycemic therapies. Some of the oral hypoglycemic drugs have contraindication or recommended dose adjustments related to renal impairment. Dose adjustment is also recommended for all DPP-4 inhibitors except linagliptin when used in patients with moderate to severe renal impairment. Linagliptin, due to its predominantly non-renal route of elimination, requires no dose adjustment.

CONCLUSION

The results from the comparative study to evaluate the efficacy and safety of linagliptin and sitagliptin drugs.

- The present study shows that two drugs such as linagliptin and sitagliptin reduced the fasting plasma glucose, post prandial plasma glucose and glycosylated haemoglobin level. But the linagliptin provided superior control of glycemic as compare to sitagliptin.
- There were no significant changes in BMI on both drugs.So linagliptin and sitagliptin had good body weight control.
- There were favorable changes in lipid profiles in that linagliptin more favorable than sitagliptin.
- Our study shows that insignificance of renal (Sr.Cr, BU, SUA) and hepatic (TB, ALT, AST) profile. So both drugs were considered to be more safe.

It can be concluded with the results of the present study linagliptin possesses greater efficacy with increased glycemic control and good safety compared to sitagliptin in Type 2 diabetic patients.

BIBLIOGRAPHY

1. Definition, Diagnosis and Classification of Diabetes Mellitus and its complications, Report of WHO consultation, World Health Organization Department of Noncommunicable disease surveillance, Geneva 1999; 1-30.
2. KirtiKaul, Joanna M.Tarr et al., Introduction to diabetes mellitus, Diabetes: An old disease, a New Insight, edited by Shamim I. Ahmad, Landes Bioscience and Springer science+Bussiness Media, 2012; 1-11.
3. Eric T.Herfindal,DickR.Gourley,Text book of therapeutics, Drug and disease management, 6th edition,Williams and Wilkins, A waverly company, 1996; 357-360.
4. William H. Herman, Diabetes Epidemiology: Guiding clinical and public health practice, The Kelly west award lecture 2006, Diabetes care. July 2007; 30(7):1912- 1919.
5. Marry Anne Koda-Kimble, Lloyd Yee Young, Brain K. Alldredge et al.,Applied therapeutics, The clinical use of drugs,9th edition. Lippincott Williams and Wilkins,2009; 50-3
6. V.Mohan, S.Sandeep, R.Deepa, B.shah and C.Varghese, Epidemiology of type 2 diabetes: Indian scenario. Indian Journal of Medical Research. March 2007; 125:217-230.
7. American Diabetes Association, Diagnosis and classification of diabetes mellitus, Diabetes care, January 2006; 29(1):S43-S48.
8. Stephen J. McPhee, Maxine A.Papadakis et al., Diabetes mellitus and hypoglycemia Current medical diagnosis and treatment,McGrawHill Lange ,2008.
9. Joseph T.Dipiro, Robert L.Talbert et al., Pharmacotherapy, A Pathophysiologic Approach 6th edition, McGraw Hill Companies, 2005; 1333-1336.
10. Screening for type 2 diabetes, Report of a World Health Organization and International Diabetes Federation Meeting, Geneva, 2003:5.
11. Sharon Brez RN et al., Monitoring glycemic control, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Canadian journal of diabetes, September 2008; 32(1):S32-S36.
12. Christopher D. Saudek,M.D.,and Jessica C. Brick, B.A.The clinical use of Hemoglobin A1c,Journal of Diabetes Science and Technology, July 2009; 3(4):629-634.
13. Diagnostic Approaches and interventional strategies of type 1,type 1.5 and type 2 diabetes:5
14. Michael J. Fowler, MD, Microvascular and Macrovascular complications of Diabetes, Clinical Diabetes, 2008; 26(2):77-82.

15. Keecia D. King,PharmD, Jocelyn D. Jones et al., Microvascular and Macrovascular complication of diabetes Mellitus, American Journal of Pharmaceutical Education,2005;69(5)Article 87:1-10.
16. Ronald Klein, Jinan B. Saaddine et al., Diabetes and vision, Diabetic Public Health, Oxford University press, 2011: 111-112.
17. Antonio Ceriello, Anselm K. Gitt, et al.,Macrovascularcomplications,DIAMAP Road Map for Diabetes Research in Europe, September 2010:137-138.
18. Helen Jones,LoriD.Berard et al., Self-management Education, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Canadian journal of diabetes, September 2008; 32(1):S25-S28.
19. Education, Global Guideline for Type 2 Diabetes, International Diabetes Federation, Clinical Guidelines Task Force, 2012:21.
20. SaurabhRamBiharialShrivastava et al.,Role of self-care management of diabetes mellitus, Journal of Diabetes and Metabolic Disorders,2013;12(14):1-5.
21. Diabetes Management in General Practice, Guidelines for Type 2 Diabetes, 18thedition, Diabetes Australia Limited, 2012/13:23-28,39,45-46.
22. RejeanneGougeon et al., Nutrition Therapy, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Canadian journal of diabetes, September 2008; 32(1):S40-S45.
23. RiethofM,FlavinPL,etal.,Diagnosis and Management of Type 2 Diabetes Mellitus in Adults, Institute for Clinical Systems Improvement, Health care Guideline, April 2012:15.
24. Ronald Sigal, Glen Kenny et al., Physical Activity and Diabetes, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Canadian journal of diabetes, September 2008; 32(1):S37-S39.
25. David M.Nathan, John B. Buse et al., Medical management of hyperglycemia in type 2 Diabetes: A consensus Algorithm for the initiation and Adjustment of therapy, Diabetes Care, January 2009; 32(1):193-203.
26. Ralph A.Defronzo,MD,pharmacologic Therapy for Type 2 Diabetes Mellitus, Annals of Internal Medicine, August 1999;131(4):281-303.
27. Michael.A.Nauck, Tina Vilsboll et al., Incretin-Based Therapies, Diabetes Care, November 2009; 32(2):S223-S231.
28. David D'Alessio,MD,DPP-4 Inhibitors:Stratergies for PPG Control, Peak Issues, Clinical Use of Incretin-Based Therapies to Treat Type 2 Diabetes, The Caring For Diabetes Educational Forum, August 2010;2:1-2.

29. Bo Ahren, MD, PhD, Dipeptidyl peptidase-4 inhibitors, Diabetes Care, June 2007; 30(6):1344-1350.
30. Maximilian Von Eynatten et al.,Efficacy and safety of linagliptin in type 2 diabetes subjects at high risk for renal and cardiovascular disease: a pooled analysis of six phase III clinical trials, Cardiovascular Diabetology,2013;12(60):1-9.
31. Janet B. McGill, et al.,Long- term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment, Diabetes care,2013;36:237-244.
32. Odd Erik Johansen et al.,Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified,prospective,and adjudicated meta-analysis of a phase 3 programme,Cardiovascular diabetology,2012;11(3):1-10.
33. Debmalya Sanyal et al.,A retrospective study evaluating efficacy and safety of linagliptin in treatment of NODAT(in renal transplant recipients)in a real world setting, Indian journal of Endocrinology and Metabolism,2013;17(1):S203-S205.
34. Erika Paniago Guedes et al., linagliptin: farmacology, efficacy and safety in type 2 diabetes treatment, Diabetology and Metabolic Syndrome, 2013; 5(25):1-7.
35. Hannele Yki-Jarvinen et al.,Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes, Diabetes Care,2013;36:3875-3881.
36. Barry J.Goldstein et al.,Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes, Diabetes Care, August 2007;30(8):1979-1987.
37. Carolina Solis-Herrera et al.,Mechanism of glucose lowering of dipeptidyl peptidase-4 inhibitor sitagliptin when used alone or with metformin in type 2 diabetes, Diabetes Care, September 2013;36:2756-2762.
38. Guillermo E.Umpierrez et al.,Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes, Diabetes Care, November 2013;36:3430-3435.
39. Jorge Luiz Gross et al.,A novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medication: an example using DPP-4 inhibitors, sitagliptin and linagliptin, in treatment of type 2diabetes mellitus,BMJ open accessible medical research,2013;3:e001844:1-11.
40. Kaustubh Nisal et al.,Comparison of efficacy between incretin- based therapies for type 2 diabetes mellitus,BMC Medicine,2012;10(152):1-10.
41. Masaya Sakamoto et al., Comparison of vildagliptin twice daily vs. sitagliptin once daily using continuous glucose monitoring(CGM):Crossover pilot study(J-VICTORIA study),Cardiovascular Diabetology,2012;11(92):1-7.

42. Roger Gadsby et al., Efficacy and safety of sitagliptin in the treatment of type 2 diabetes, Clinical Medicine: Therapeutics, 2009; 1:53-62.
43. Akira Kanamori et al.,Factors associated with reduced efficacy of sitagliptin therapy: Analysis of 93 patients with type 2 diabetes treated for 1.5 years or longer, Journal of Clinical Medicine Research,2013;5(3):217-221.
44. EleFerrannini et al., Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin, Diabetes Care, 2013; 36:4015-4021.
45. GuntramSchernthaner et al.,Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea, Diabetes Care, September 2013;36:2508-2515.
46. Ralph A.Defronzo et al.,The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone, Diabetes Care,2009;32:1649-1655.
47. MuthukrishnanJayaraman et al., Acute pancreatitis with gliptins: Is it a clinical reality, Indian Journal of Endocrinology and Metabolism, 2013; 17(1):S323-S325.
48. Robert Frederich et al., The efficacy and safety of the dipeptidyl peptidase-4 inhibitor saxagliptin in treatment-naïve patients with type 2 diabetes mellitus: a randomized controlled trial, Diabetology and Metabolic Syndrome, 2013; 4(36):1-12.
49. Iftekar H et al.,Efficacy and safety of vildagliptin in the management of type 2 diabetes mellitus, Indian journal of pharmacy practice,2012;5(4):7-15.
50. htt//www.drugbank.com
51. htt//www.druugs.com